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Critique of Chapter 4

Smoking Lower Yield Cigarettes and Disease Risks
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A. Introduction

The introduction of this chapter defines the primary question the chapter will address and discusses the methodologies that will be used to reach an answer to that question. The authors state that, "[T]his chapter is focused on answering the question: 'Have changes in cigarette manufacture and design over the last 50 years resulted in a meaningful public health benefit to human smokers?' " The authors subdivide this question into "two related but distinct research questions." These two research questions are, "[F]irst has the risk per cigarette smoked been changed by these product modifications; and second have the net adverse consequences of smoking for the population been changed by these product modifications." It is extremely important to understand the difference between these two research questions, in that it goes to the heart of not only this chapter but the entire document. The first question can be rephrased as follows: if a cigarette delivering lower machine-determined tar were to be smoked in exactly the same manner for the same duration and in identical amounts to a cigarette delivering higher machine-determined tar, would the smoker be at lower risk for smoking associated disease? The second question can be rephrased: are individuals who smoke cigarettes with lower machine-determined tar at lower risk for smoking associated disease in the 'real world' than they would have been had they smoked cigarettes with higher machine-determined tar? It is clearly the second question that is of practical relevance.

The authors pose this latter research question in another manner in the first paragraph of the introduction:

> "No cigarette currently manufactured and sold can be considered safe, and the principal recommendation for any smoker interested in reducing future disease risks is to quit smoking. However, approximately 47 million individuals remain cigarette smokers in the United States (CDC, 2000a), and many of these smokers have tried to quit and failed. If these continuing cigarette smokers could alter their risks by choosing cigarettes that differ in machine-measured tar and nicotine yields or other characteristics, and if this choice did not interfere with their likelihood of cessation, then advice to switch brands might be one component of a comprehensive strategy to reduce the disease consequences of tobacco use. Alternatively, if these lower yield products do not reduce risks and if smokers switch brands instead of quitting, then the changes in cigarettes and their marketing as reduced-risk products represent a cruel deception of current smokers."

There are two points made in the quotation above. The first is, can smokers "alter their risks by choosing cigarettes that differ in machine-measured tar and nicotine yields or other characteristics." The second is does this choice "interfere with their likelihood of cessation." Only the first of these points is addressed in Chapter 4. Therefore, this is the issue that will be specifically addressed in this review.

Chapter 4 utilizes three main sources of data to determine if cigarettes that are lower in machine-measured tar and nicotine yields have actually reduced the risk of smoking associated diseases. These three sources of data are: (1) case-control and cohort studies that have compared lung cancer risks in smokers of different types of products at particular points and times, (2) comparison of lung cancer rates in smokers over time, coming from either a single cohort with a lengthy follow-up or repeated cohort observations, and (3) observations of national rates of lung cancer by age in relation to age-specific smoking patterns. As the authors point out each one of these sources of

data has strengths and limitations. However, the authors and we agree that should these three sources of data present a reasonably consistent result, one is more able to rely on this result compared to a result from only one single source of data. The introduction does state, however, that greater weight was placed on evidence derived from trends in populations over time than on evidence from epidemiological studies, since reductions in general population death rates are the ultimate outcome measure for the effect of changing cigarette design over the last 50 years.

The goal of this analysis will be to examine the authors' treatment of each one of these sources of data to determine if the conclusions they reach are truly supported by the data that they utilize as well as relevant data that the authors have not used.

B. Historical Development of the Lower Yield Cigarette Issue

The next section of Chapter 4 provides a brief discussion of the historical development of the lower yield cigarette. Much of this information is simply a review of material that was presented in Chapters 2 and 3 of this monograph. However, some of it is quite relevant to the further discussions within Chapter 4 and will therefore be discussed herein.

The authors point out that it was a logical extension of those early epidemiological studies that established the epidemiological association between cigarette smoking and lung cancer to assume that reduction in the "dose" of particulate matter received by the smoker would also reduce the risk of lung cancer. This "logical extension" has been confirmed in essentially every epidemiological study on smoking and lung cancer, since the relative risk for lung cancer is clearly and strongly dependent on the number of cigarettes smoked per day. As a consequence of the dose dependence of cigarette smoke with lung cancer, "[I]ndependent scientists and public health authorities recommended that cigarettes which reduced tobacco smoke delivery to the smoker be developed and marketed by tobacco companies." Such cigarettes were indeed developed and marketed. However, it is undeniably the fact that reduction in smoke delivery achieved was determined through machine smoking using the FTC (in the US) protocol.

Clearly, as the authors point out, "[B]oth the smoke exposure and the disease risks resulting from smoking lower yield cigarettes depend on how these cigarettes are used by smokers." It is equally obvious that different smokers will and do smoke differently, and it is also equally obvious that a very small minority of smokers will have smoking parameters that are close to those specified by the FTC protocol. Moreover, as indicated above, both smoke exposure and disease risk are a function of the number of cigarettes smoked per day. This latter point, as will be seen, is of crucial importance to many of the issues discussed in Chapter 4. Therefore, it is essential to determine either smoke exposure or disease risk in an objective manner in order to be able to establish if reduction in tar and nicotine yields translate into an actual decrease in the risk of smoking-related disease.

As indicated in the discussion above concerning the Introduction, Chapter 4 focuses on data that address reduced risk potentially resulting from a decrease in nominal smoke yields. This section of Chapter 4 is the only section that deals with smoke exposure. The discussion herein is based completely on internal company documents and it purports to show that: (1) industry scientists were aware of the fact that smoke exposure may not be reflected by smoke yield as measured by the FTC protocol; (2) studies carried out by industry scientists demonstrated that there was no reduction in human exposure for smokers who smoked lower yield cigarettes; and (3) that cigarettes were deliberately designed by tobacco companies that would give low machine yields but considerably higher human smoke exposure. With respect to the first point it is certain that more than one industry scientist has asked the question – sometimes in writing – as to whether smokers of low yield cigarettes "compensated" sufficiently to eliminate any reduction in actual exposure provided by lower delivery cigarettes. With respect to the second point, a number of studies have been carried out by industry scientists to assess actual smoke exposure. These studies have without exception been too small and suffered from a number of design flaws to

provide any meaningful results. This is the reason that Philip Morris decided to proceed with the currently planned total exposure study. Lastly, it would appear that the original Barclay cigarette was indeed designed explicitly by Brown and Williamson and BAT to give low machine yields but much higher smoker yields. However, I am not aware of any other cigarette of this type that has been marketed. Suffice it to say, and the review of Chapter 3 clearly demonstrates, that Philip Morris scientists accept that some degree of compensation does take place, but that there is no existing study that has been sufficiently well designed to determine to what degree. As indicated, this gap will be filled by the total exposure study.

In the closing paragraphs of this section the authors point out that despite the fact that internal company documents questioned the possible impact of lower delivery cigarettes on actual smoke exposure, early studies of the disease risks among smokers of low-yield cigarettes were encouraging. However, the authors then state that, "[A] reduction in U.S. lung cancer death rates of the magnitude expected from the differences in risk found in epidemiological studies of lower yield cigarettes (15-40%) has not been realized. Lung cancer death rates have continued to rise among women, and the modest decline in lung cancer death rates observed among men is generally consistent with the temporal trends of reduced initiation and increased cessation among males." Two references were cited in support of this statement (Tolley et al., 1991; Mannino et al., 2001). It is of crucial importance to note that, as the authors indicated, this statement refers to the U.S. situation. The authors then refer to the well-publicized findings of the two large American Cancer Society studies, CPS-I and CPS-II. "In addition, two studies performed by the American Cancer Society 20 years apart (1960s vs. 1980s) have shown an increase in lung cancer risk among current smokers. In these studies, there was no evidence for any decline in lung cancer risk, even when the subjects were compared controlling for number of cigarettes smoked per day, duration of smoking, and age." Again this finding is specific to the US, despite the fact that the authors suggest that this result was confirmed by results from the second 20 years of follow up from the British Physicians study.

As a consequence when the authors refer, in the last paragraph, to the "...discrepancies between epidemiological studies demonstrating reductions in risk with the use of low-yield and filtered cigarettes and the absence of population-based reductions in the hazards of smoking...", this analysis will show that these discrepancies may well be unique to the US situation. Moreover, recent data from the US suggests that the situation with respect to national lung cancer death rates as depicted by Burns, et al., may well be changing. However, this discussion will be deferred to until later in the analysis, as we will continue to follow the narrative path of Chapter 4 that proceeds to discuss in some detail epidemiological data obtained from cohort and case-control studies. The goal of this discussion is to "...resolve the apparent differences between published epidemiological evaluations and the mortality experience in the United States."

C. Limitations of Epidemiological Studies in Examining the Risks of Low-Yield Cigarette Use

This section devotes considerable discussion to the fundamental problems involved in carrying out meaningful epidemiological studies directed toward resolving the question as to whether lower delivery cigarettes are associated with lower disease risk. The points raised in this discussion are well known and are issues in any epidemiological study. The authors also point out that, "[T]he tools used by epidemiologists are rather blunt..." This is also well known. It is a consequence of the fact that the tools of epidemiology are blunt that multiple epidemiological studies that give reasonably consistent results are required before scientists are willing to accept such results. Moreover, particularly in cases where the epidemiological relative risk is weak (e.g., less than 2 or 3) ancillary evidence, such as the Bradford Hill aspects (Bradford Hill, 1965), is used to provide assurance that the epidemiological results are meaningful. This analysis clearly agrees with the points that Burns, et al., raise regarding the epidemiology, and also agree that such results have to be interpreted with considerable caution. These points will be discussed further below.

The important portion of this section is contained in the last two paragraphs. The authors state in the first sentence of the penultimate paragraph that, "[T]he principal determinant of the chronic disease risk associated with smoking is the amount of tobacco smoke to which an individual is exposed as measured by the intensity and duration of smoking." The paragraph then goes on to reiterate the effect that compensatory behaviors may have on smoking "intensity." This paragraph ends as follows:

> "Compensatory behaviors may include: 1) taking more frequent puffs per cigarette; 2) taking larger puff volumes and inhaling more deeply; 3) obstructing the ventilation holes that would otherwise dilute the mainstream smoke; and 4) smoking more cigarettes per day. Thus the FTC tar and nicotine ratings do not accurately reflect the exposure of an individual smoker to the carcinogens in tobacco smoke, as they do not take account of any of these compensatory behaviors."

It is clearly correct that FTC tar and nicotine ratings do not accurately reflect the exposure of an individual smoker. However, it is of extreme importance to point out that epidemiological studies designed to assess a potential decrement of disease risk as a function of cigarette delivery do address at least three of these compensatory behaviors. Since one is simply comparing disease risks in smokers of cigarette A to cigarette B, the fact that smokers of cigarette A may have taken more frequent puffs, inhaled more deeply, or blocked ventilation holes is automatically considered. If one obtains a lower relative risk for lung cancer for cigarette A, then this lower relative risk was achieved despite the fact that the smoker of cigarette A may, or may not, have engaged in any or all of such compensatory behaviors. This of course suggests that if the smoker of cigarette A did compensate, that the relative risk would have been even lower had he not compensated.

The one type of compensatory behavior that may influence the relative risk is if smokers of lower delivery cigarettes smoke a greater number of cigarettes per day. Clearly, Burns, et al., recognize this, since it is the issue of number of cigarettes per day that they use to explain the inconsistency of the epidemiological results with what they term the "mortality experience in the United States." This issue will be discussed at considerable length in Sections E-N.

D. Comparing Populations of High- and Low-Yield Cigarette Smokers in Epidemiological Studies – Population Differences

Before moving on to a very detailed discussion regarding the potential effect of compensation by cigarettes per day with respect to the epidemiological data, the authors briefly discuss possible confounders that could bias or explain the observed reduction in the risk for lung cancer found in many epidemiological studies that compare smokers of lower delivery cigarettes with smokers of higher delivery cigarettes. The basis of their argument is that smokers commonly understand that smoking of low-tar products results in less risk. Therefore, individuals who choose to switch to low-tar products (or filter cigarettes in early epidemiological studies) are likely to be those smokers who are more health conscious. Data from the California Tobacco Survey (1998) indicate that use of lower delivery products increase with age, education, and income and is higher among females than males. Similar differences across type of cigarette smoked were evident in a national sample of smokers (Giovino, et al., 1996). The authors point out that, "[T]he higher educational and socioeconomic status of low-yield cigarette smokers are likely to be correlated with other positive health behaviors (diet, exercise, etc.) that may lower disease risk for reasons independent of choice of cigarette type."

The authors also point out that, "these same low-yield cigarette smokers may also have higher rates of successful long-term smoking cessation or may voluntarily reduce the amount that they smoke for health reasons." Should such individuals relapse, it is not unreasonable to assume that such individuals would be more likely to smoke lower yield cigarettes.

Another potential confounding factor discussed is the role of level of addiction. As the authors state:

> "It is also possible that less-intense and less-addicted smokers may either use, or be more likely to successfully switch to, low-yield cigarettes. Their demand for nicotine is less, and it may be more easily satisfied by cigarettes that deliver less nicotine. In contrast, heavy smokers and those who are strongly dependent may not be able to extract sufficient nicotine from these lower yield products to satisfy their addiction, so they may preferentially choose higher yield cigarettes."

A single potential confounding factor is mentioned that could understate the decline in risk observed for lower tar smokers. Smokers with newly diagnosed disease who are unable to quit may switch to low-yield cigarettes in the belief that there is less risk associated with their use. This would have the effect of an apparent increase in disease rates for low-delivery smokers.

There is no question that confounding can have a significant effect on the magnitude of an epidemiological relative risk when such relative risks are less than 2 or 3. Relative risks observed for lung cancer, for example, for smokers of non-filter (or high-tar) cigarettes compared to smokers of filter (or low-tar) cigarettes are generally less than 2. As a consequence, we agree with the authors that the potential confounding effects that they mention could be important. Published studies do not allow for any possible estimate of the magnitude of such potential confounding effects.

A more detailed discussion of potential confounding will be provided later. Several general comments can be made at this point. First, the argument that the authors use above, that "less-intense and less-addicted smokers" have less of a demand for nicotine and "may be more easily satisfied by cigarettes that deliver less nicotine," implies that such smokers are not likely to increase their smoking after switching to a lower nicotine (and lower tar) product. This argument is in complete opposition to the next several sections of Chapter 4, where the authors attempt to demonstrate that individuals who switch to lower delivery cigarettes actually increase the number of cigarettes per day smoked. Secondly, there is an extremely important potential bias in published studies, albeit not a confounder, that would be expected to significantly understate the differences in risk between smokers of higher and lower delivery cigarettes. This is the fact that the most smokers of filter, or low delivery, cigarettes who have developed (case-control studies) or do develop (cohort studies) lung cancer, were not exclusive smokers of such cigarettes. The vast majority switched at some point. Therefore, any difference in risk that was observed in an epidemiological study is actually lower than would be expected if two groups of smokers where no switching occurred were being studied. Although the authors mention this point in an earlier section, they do not mention it in this section as a factor that would understate the decrease in risk observed.

Lastly, it should be mentioned that confounding is often mentioned by groups who are not in agreement with the results of a set of epidemiological studies. It was the published opinion of at least one epidemiologist (Hertz-Picciotto, 2000) that if a weak epidemiological association appears to be supported by other evidence (e.g., the Bradford Hill aspects), it is the responsibility of those individuals who claim that confounding could account for the observed association to demonstrate such a claim through published studies.

E. Using Number of Cigarette Per Day to Control for Intensity of Smoking in Epidemiological Studies

This short section discusses in some detail the issue of how adjustment for cigarettes smoked per day can result in an apparent decrease in risk in an epidemiological study that compares lower delivery cigarettes to higher delivery cigarettes when no such decrease in risk actually exists for the smoker. The essence of this discussion is captured by the graph on page 79. This graph, not

based on actual data, plots relative risk as a function of number of cigarettes smoked per day for both "high-tar" and "low-tar" cigarettes. The slope for the "high-tar" cigarette is steeper than is the slope for the "low-tar" cigarette. In other words, based on the author's graph, the relative risk for an unspecified smoking-related disease would be lower for a smoker of a "low-tar" cigarette compared to a smoker of a "high-tar" cigarette, assuming both individuals smoked exactly the same number of cigarettes per day.

The authors state that, "a smoker who compensates fully could do so by either exclusively changing the pattern of smoking or by increasing the number of cigarettes smoked per day as part of that compensation. If a smoker compensates entirely by changing the pattern of smoking and does not increase the number of cigarettes smoked per day, the smoker will drop vertically from the high-tar line to the low-tar line. If the level of compensation is only partial, this smoker would experience a reduction in the daily smoke dose received, and one would expect a population of smokers who had this form of partial compensation to have lower lung cancer rates."

It is important to analyze the above statements in more detail. The first point is that the authors believe, as do we, that the risk for lung cancer is a function of the total tar inhaled. This amount of total tar can be viewed as being related to the number of cigarettes smoked per day, smoking duration (up to a given age), or the yield from each cigarette that the smoker receives.

The second point deals with the first sentence above. This sentence states that "a smoker who compensates fully could do so by either..." It should be noted that the issue is not full compensation. No difference in relative risk would be expected between a smoker of a "high-tar" cigarette and the smoker of a "low-tar" cigarette who fully compensates by whatever combination of mechanisms. Consequently, when the authors state in the next sentence, "[I]f a smoker compensates entirely by changing the pattern of smoking and does not increase the number of cigarettes smoked per day..." they are referring to smokers who compensate less than fully. This point is indeed made in the following sentence, where the authors state, "[I]f the level of compensation is only partial..."

This sentence is the subject of the third point. The authors make it clear that any compensatory behavior, besides the number of cigarettes smoked per day, will be automatically taken into account by the epidemiologically determined relative risk. An example easily illustrates this point. If an epidemiological study finds a relative risk for lung cancer of 0.7 for smokers of filter cigarettes compared to smokers of non-filter cigarettes, this represents a real decrease in risk for the smoker. Since it is impossible to correct for any possible increase in puff number, depth of inhalation, puff frequency, etc., the decrease in relative risk is what the smoker actually experienced no matter what form of compensatory smoking behavior with respect to how the cigarette was smoked. This point was made quite clearly by one the co-authors of this Chapter in Monograph No. 7 (Samet, 1994).

The last point the authors make is correct, at least in principle, that if a smoker increases the number of cigarettes smoked per day, an epidemiologically determined decrease in relative risk may not be what the smoker actually experienced. Again, an example can illustrate this point. Once again, an epidemiological study finds a relative risk of 0.7 for smokers of filter cigarettes (e.g., 15 mg tar/cigarette) compared to smokers of non-filter cigarettes (e.g. 24 mg tar/cigarette) adjusted so that equal numbers of cigarettes per day are being smoked by both groups of smokers. However, if the smokers of filter cigarettes increase the number of cigarettes smoked per day by 60%, they would actually be exposed to the same amount of tar as the smokers of the non-filter cigarettes, and no difference in actual disease risk would be expected, despite the observed 30% decrease in relative risk.

The authors point out that many of the published epidemiological studies (although not all) of low-yield cigarettes have adjusted for the number of cigarettes per day. They conclude, based on the analysis discussed above, that, "a number of cautions are appropriate when examining

epidemiological data on disease risks among those who smoke cigarettes with different machine-measured tar and nicotine yields...[because] control for intensity of smoking across populations using number cigarettes smoked per day as the measure of dose may result in model misspecification if smokers who switch to low-yield cigarettes compensate by increasing the number of cigarettes per day."

The following section contains a discussion of the results from published epidemiological studies on the association of machine-measured reduction of tar and nicotine with lung cancer risk. A thorough analysis of the data will allow this review to determine whether or not it is appropriate to conclude that the observed reduction in risk is eliminated by a concomitant increase in number of cigarettes smoked per day.

F. Published Epidemiological Studies of Health Endpoints – Lung Cancer

Table 4-1 in this section lists studies that have examined lung cancer risks with low yield products. The authors state:

> "While a few studies have not found a relationship, and several of the relationships identified were not statistically significant, the clear impression from these studies taken as a whole is that there is a lower risk of lung cancer among populations of smokers who use lower yield products. This relationship is evident in case-control studies as well as in prospective mortality studies."

The authors then go on to state that, "the vast majority of these studies controlled for intensity of smoking using the number of cigarettes smoked per day." Following a discussion of the results of two of these studies, the authors conclude this section as follows:

> "In summary, most case-control and prospective mortality studies conducted in different geographic locations demonstrated differences in lung cancer risks for filter and low-tar (machine-measured) smokers compared with nonfilter and high-tar smokers when controlled for cigarettes smoked per day. The question that remains is whether differences in lung cancer experience are due to differences in machine-measured tar yield of the cigarettes smoked, due to difference in other characteristics of the smokers who use these products, or due to differences introduced by model misspecification in these studies."

Before a discussion directed at how the authors answer this question, it is worthwhile to first analyze the studies themselves to determine what effect, if any, adjustment for cigarettes per day have with respect to the reported relative risk. The studies cited by the authors in their Table 4-1 are listed in Tables 1 and 2. Table 1 considers those studies that compared lung cancer risk for filter and non-filter cigarette smokers and provides relative risks (RRs) or odds ratios (ORs) for fitter vs. non-filter. Table 2 considers those studies that attempted to determine the relationship of lung cancer relative risk with tar yield and provides RRs or ORs for low tar vs. high tar. Table 1A and Table 2A list studies considered in Chapter 4. In addition to the studies listed by the authors a number of other relevant studies have been included. These studies were obtained from a recent paper by Peter N. Lee (2001) and are listed in Tables 2A and 2B. Several references are also included in Table 2B deriving from studies published or translated following the Lee paper. It should be noted that all relevant studies listed by the authors were also considered by Lee. In some cases there are multiple publications of results from the same study. In such cases we have attempted to utilize the results from the publication that provides the most complete results.

For each study the following information is listed: 1) authors, date of publication, and journal reference; 2) a short description of the study; 3) the time period covered by the study; 4) the RR or OR unadjusted for cigarettes per day; 5) the RR or OR adjusted for cigarettes per day; and 6) any relevant remarks.

Table 1A
Epidemiological Studies of Filter Cigarettes vs. Non-Filter Cigarettes for Lung Cancer
Citations Taken from Monograph No. 13

Citation	Population	Time Period	RR or OR Unadjusted for Cigts./Day	RR or OR Adjusted for Cigts./Day	Remarks
Bross, I. D., and Gibson, R., *Am. J. Public Health*, 58(8): 1396-1403, 1968	Case-control study of 974 white male lung cancer patients and hospital controls	1960-1966	0.59 (M) 95% CI, 0.40-0.88	0.57 (M) 95% CI, 0.39-0.85	The data are stratified by smoking duration and a rough indication of cigts./day. The OR of 0.59 is based on the total sample and is therefore unadjusted for cigts./day.
Bross, I. D., National Cancer Monograph No. 28, *Toward a Less Harmful Cigarette*, U. S. DHEW, NCI, 1968					This publication covers the same study by Bross and Gibson noted above and the data published are identical.
Lee, P. N., and Garfinkel, L., *J. Epidemiol. Community Health*, 35: 16-22, 1981	Review of 9 studies, three prospective studies, and 6 case-control studies	1959-1979			This is a review article with a pooled relative risk. References cited are included in this analysis.
Hawthorne, V. M., and Fry, J. S., *J. Epidemiol. Community Health*, 32: 260-266, 1978	Prospective follow-up of 18,786 people attending a multiphasic screening examination	1965-1977		0.83 (M) 95% CI, 0.53-1.31	The number cited is the ratio of relative mortality in this study for filter smokers compared to non-filter smokers. Relative mortalities have been adjusted for age, and cigarettes per day.
Todd, G. F. et al., *Journal Epidemiol. Community Health*, 32: 267-274, 1978.	12.4-year prospective follow-up of 10,063 subjects aged 35-69 from a random sample of the population in Great Britain	1965-1977			This paper provides considerably less data than an analysis carried out on the same study by Reid cited in the Lee and Garfinkel review (1981). These data are listed in Table 1B.

Citation	Population	Time Period	RR or OR Unadjusted for Cigts./Day	RR or OR Adjusted for Cigts./Day	Remarks
Engeland, A., et al., *Cancer Causes and Control*, 7: 366-276, 1996	A prospective study of 26,126 Norwegian men and women drawn from a population sample	1966-1993	0.53 (M) 95% CI, 0.24-1.18 0.58 (F) 95% CI, 0.25-1.34	0.67 (M) 95% CI, 0.30-1.43 0.91 (F) 95% CI, 0.40-2.00	Unadjusted RRs are calculated from data published in the citation. Adjusted RRs included terms for cigarettes per day, age, occupational exposure, rural or urban living, and perhaps other factors. The model is not completely specified. Table 2 of this reference clearly indicates that, for both males and females, smokers of factory-made filter cigarettes only smoked fewer cigarettes per day than smokers of factory-made non-filter cigarettes.
Tang, J.-L., et al., *BMJ*, 311: 1530-1533, 1995	Four prospective mortality studies from the United Kingdom	1967-1982		0.94 (M) 95% CI, 0.75-1.18	Adjusted for cigarettes per day, age, and study. Data are not available to calculate unadjusted relative risk. Also see Table 2A.
Wynder, E. L., et al., *JAMA*, 213: 2221-2228, 1970; Wynder, E. L., *Cancer*, 30: 1332-1339, 1972.	Case-control study of 350 lung cancer patients and approximately 700 controls	1966-1969	0.52 (M) 95% CI, 0.35-0.76	0.51 (M) 95% CI, 0.34-0.76	The data cited are derived from the 1972 reference, but both publications cover the same study. The OR unadjusted for cigarettes per day is completely unadjusted. The OR adjusted for cigarettes per day is also adjusted for age.

Citation	Population	Time Period	RR or OR Unadjusted for Cigts./Day	RR or OR Adjusted for Cigts./Day	Remarks
Wynder, E. L., and Stellman, S. D., *J. Natl. Cancer Inst.*, 62: 471-477, 1979	Case-control study of 684 lung cancer patients and 350 larynx cancer patients	1969-1976	0.76 (M) 95% CI, 0.59-0.98 0.74 (F) 95% CI, 0.40-1.40	0.77 (M) 95% CI,0.59-0.99 0.73 (F) 95% CI, 0.39-1.39	Although the adjusted data are grouped by category of cigarettes per day smoked, overall ORs, adjusted for cigarettes per day can be calculated from the data and these are listed in the table. Unadjusted ORs are calculated from Text-Figure 1.
Kabat, G. C., *Lung Cancer*, 15: 1-20, 1996	Case-control study of 7,553 lung cancer cases and 19,992 hospital controls. This study is a continuation of the Wynder and Stellman study cited above.	1969-1991			This report is an earlier report of the same case-control study reported on by Stellman below (Stellman, *Cancer*, 80: 382-388, 1997). Therefore, only the Stellman results will be included in the meta-analysis.
Rimington, J., *Environ. Res.*, 24: 162-166, 1981	Follow-up study of 2,393 non-filter and 3,045 filter cigarette smokers from a sample of mass radiography volunteers aged 40 or more in England	1970-1976	0.65 (M) 95% CI, 0.44-0.96	0.62 (M) 95% CI, 0.42-0.91	The unadjusted OR is calculated from data presented by the authors. The adjusted OR is calculated from data presented by category of cigarette per day. All ORs are adjusted for age.
Lubin, J. H., *Brit. Med. J.*, 288: 1953-56, 1984; *Brit. Med. J.*, 289: 921, 1984	Case-control study of 7,181 lung cancer patients and 11,006 hospital controls in five Western European countries	1976-1980			This publication provides data on a subset of the Lubin, et al., study (*Int. J. Cancer*, 1984) noted below. Therefore, only the results of this larger study will be included in the meta-analysis.

Citation	Population	Time Period	RR or OR Unadjusted for Cigts./Day	RR or OR Adjusted for Cigts./Day	Remarks
Lubin, J. H:, et al., *Int. J. Cancer*, 33: 569-576, 1984	A case-control study of 7,804 cases and 15,207 hospital-based controls in seven Western European locations	1976-1980	0.66 (M) 95% CI, 0.57-0.76 0.52 (F) 95% CI, 0.34-0.82	0.48 (M) 95% CI, 0.40-0.56 0.43 (F) 95% CI, 0.22-0.85	Unadjusted OR calculated from data provided in citation. OR adjusted for cigarettes per day also adjusted for years since quit. Citation also contains data on high-tar/low-tar comparisons.
Benhamou, S., et al., *J. Natl. Cancer Inst.*, 74: 1169-1175, 1985	Case-control study of 1,625 lung cancer patients and 3,091 hospital controls. This report includes males excluding those who smoked other forms of tobacco -- 1334 cases and 2409 controls	1976-1980			This study is an earlier report of the 1994 publication (*Int. J. Epidemiol.*, 24: 437-443, 1994). Therefore, only the later results will be used in the meta-analysis.
Buffler, P. A., et al., *Annual Clinical Conference on Cancer*, 28: 27-34, 1986	Case-control study of 476 cases and 466 population-based controls.	1976-1980	0.92 (M) 1.17 (F)		ORs are not adjusted for any cofactor. No confidence limit was provided for these ORs, therefore, they cannot be included in the meta-analysis.
Benhamou, E., et al., *Br. J. Cancer*, 55: 91-95, 1987	Case-control study of 1,625 lung cancer patients and 3,091 hospital controls. This report includes females only – 96 cases and 192 controls	1976-1980	0.16 (F) 95% CI, 0.04-0.61 comparing less than or equal to 50% non-filter to 100% non-filter	0.28(F) 95% CI, 0.05-1.47 comparing less than or equal to 50% non.filter to 100% non-filter	Unadjusted OR derived from authors' univariate analysis. OR adjusted for number of cigarettes per day is also adjusted for duration of smoking, and depth of inhalation.

Citation	Population	Time Period	RR or OR Unadjusted for Cigts./Day	RR or OR Adjusted for Cigts./Day	Remarks
Benhamou, E., et al., *Brit. J. Cancer*, 60: 601-604, 1989	Case-control study of 1,625 lung cancer patients and 3,091 hospital controls. This report is for males only, but excludes that part of the sample where either the case, or both matched controls were non smokers or smoked other forms of tobacco.	1976-1980			In that this study is a subset of the study cited above (Benhamou, *J. Nat. Cancer Inst.*, 74: 1169-1175, 1985), the results are not included in the meta-analysis. The unadjusted OR comparing filter to non-filter smokers was 0.64, in good agreement with the 0.60 in the earlier publication, and the adjusted OR 0.7, somewhat less than the 0.81 cited in the earlier publication.
Benhamou, S., et al., *Int. J. Epidemiol.*, 24: 437-443, 1994	Case-control study of 1,625 lung cancer patients and 3,091 hospital controls.	1976-1980	0.38 (M) 95% CI, 0.24-0.62	0.63 (M) 95% CI, 0.35-1.10	The OR unadjusted for cigarettes per day is taken from the authors' Table 2 and is adjusted for age. The OR adjusted for cigarettes per day is taken from the authors' Table 3 and is also adjusted for age, duration of smoking, tobacco type, and socioeconomic status. This study also presents data on high-tar/low-tar.
Benhamou, E., and Benhamou, S., *Eur. J. Cancer*, 29A: 1778-1780, 1993	Combination of four case-control studies in Cuba, France, Uruguay, and Italy	1976-1988		0.91 (M)	Adjusted for age, residence, daily consumption, current smoking and type of tobacco. No confidence limit was provided for this OR, therefore, it cannot be included in the meta-analysis.

Citation	Population	Time Period	RR or OR Unadjusted for Cigts./Day	RR or OR Adjusted for Cigts./Day	Remarks
Lange, P., et al., *Eur. Respir. J.*, 5: 1111-1117, 1992	6,5111 men and 7,703 women selected randomly after age stratification from the general population in Copenhagen, followed for 13 years	1976-1989	0.82 (M) 95% CI, 0.47-1.44 0.61 (F) 95% CI, 0.21-1.79	0.90 (M) 95% CI, 0.60-1.40 0.70 (F) 95% CI, 0.40-1.40	The RRs unadjusted for cigarettes per day are adjusted for age. The adjusted RRs are adjusted for age and consumption as measured in pack years.
Alderson, M. R., et al., *J. Epidemiol. Community Health*, 39: 286-293, 1985	Case-control study of 12,693 in-patients	1977-1982	1.01 (M) 95% CI, 0.56-1.85 0.80 (F) 95% CI, 0.49-1.30	1.48 (M) 95% CI, 0.81-2.69 0.85 (F) 95% CI, 0.52-1.38	Unadjusted ORs were calculated from the numbers of cases and controls provided in the paper. Adjusted ORs were adjusted for age and number of cigarettes smoked 3 years before admission.
Wynder, E. L, and Kabat, G. C., *Cancer*, 62: 1223-1230, 1988	Case control study of 1,278 Kreyberg I patients and 2,408 hospital controls and 807 Kreyberg II patents and 1,543 matched controls	1977-1984			This study is a subset of the study reported above by Kabat (*Lung Cancer*, 15: 1-20, 1996), and therefore it should not be included in a meta-analysis. The ORs are essentially identical to those reported in the later study. This study also reports on high-tar/low-tar and is included in Table 2A.
Stellman, S. D., et al., *Cancer*, 80: 382-388, 1997	Case-control study of 1,442 male and 850 female lung cancers and 1343 hospital controls	1977-1995	0.69 (M) 95% CI, 0.51-0.94 0.63 (F) 95% CI, 0.39-1.01	0.92 (M) 95% CI, 0.65-1.29 0.68 (F) 95% CI, 0.39-1.19	Unadjusted ORs were calculated from the numbers of cases and controls provided in the paper and are combined for squamous cell cancer and adenocarcinoma. ORs adjusted for cigarettes per day were also adjusted for age and education.

Citation	Population	Time Period	RR or OR Unadjusted for Cigts./Day	RR or OR Adjusted for Cigts./Day	Remarks
Sidney, S., et al., *Cancer Causes Control*, 4: 3-10, 1993	Prospective follow-up of 79,946 Kaiser Permanente Medical Care group members for an average of 5.6 years	1979-1985	1.15 (M) 95% CI, 0.68-1.94 0.44 (F) 95% CI, 0.22-0.88	1.03 (M) 95% CI, 0.61-1.75 0.65 (F) 95% CI, 0.32-1.31	RRs unadjusted for cigarettes per day are adjusted for age. RRs adjusted for cigarettes per day are also adjusted for age, race, education, and number of years smoking. Data presented on RR as a function of tar level are in Table 2A.
Pathak, D. R., et al., *J. Natl. Cancer Inst.*, 76: 597-604, 1986	Case-control study of 521 lung cancers and 769 controls matched for age, sex, and ethnicity	1980-1982		0.80	Adjusted for age, sex, ethnic variables, amount smoked, and duration. No confidence limit was provided for this OR, therefore, it cannot be included in the meta-analysis. The OR for Hispanics was 0.04.
Khuder, S. A., et al., *Lung Cancer*, 22: 15-21, 1998	Case-control study of 482 male lung cancer cases and neighborhood controls	1985-1987	0.46 (M) 95% CI, 0.36-0.59		This OR is not adjusted for cigarettes per day, or for any other factor, in that it is clearly the result obtained from the 2 X 2 table of cases and controls. In addition, the author does not specify that the ORs were adjusted.
Armadans-Gil, L., et al., *Int. J. Epidemiol.*, 28: 614-619, 1999	Case-control study of 325 male lung cancer patients and age-matched hospital controls	1986-1990	0.43 (M) 95% CI, 0.27-0.67	0.41 (M) 95% CI, 0.30-0.70	Unadjusted OR is calculated from numbers of controls and numbers of cases. Adjusted OR is adjusted for age, smoking duration, daily cigarette consumption, and socioeconomic status.

Citation	Population	Time Period	RR or OR Unadjusted for Cigts./Day	RR or OR Adjusted for Cigts./Day	Remarks
Pezzotto, S. M., et al., *Cancer Causes and Control*, 4: 231-237, 1993	Case-control study of 215 lung cancers and 433 hospital controls	1987-1991	0.23 (M) 95% CI, 0.16-0.34	0.29 (M) 95% CI, 0.20-0.42	OR unadjusted for cigarettes per day, provided by the authors, is adjusted for age and hospital of admission. Adjusted OR, also provided by the authors, is adjusted for age, hospital of admission, and intensity and years of smoking.
De Stefani, E., et al., *Cancer Epidemiol. Biomarkers Prevention*, 5: 515-519, 1996	Case-control study of 497 cases and 497 hospital controls	1988-1994	0.72 (M) 95% CI, 0.54-0.96		Although the OR was not adjusted for cigarettes per day, it was adjusted for age, residence, urban/rural status and education.
Agudo, A., et al., *Int. J. Cancer*, 59: 165-169, 1994	Case-control study of 101 women with lung cancer with two matched hospital controls per case	1989-1992	0.22 (F) 95% CI, 0.04-1.27		The OR cited is adjusted for age, hospital, and residence.
Matos, E., et al., *Lung Cancer*, 21: 155-163, 1998	Case-control study of 200 male lung cancer patients and 397 hospital controls	1994-1996	1.49 (M) 95% CI, 0.86-2.57	1.25 (M) 95% CI, 0.67-2.50	Unadjusted OR calculated from published cases and controls for squamous cell cancer and adenocarcinoma combined. Adjusted OR adjusted for smoking status, number of cigarettes per day, duration of smoking, age of start, type of tobacco, age group, and hospital. OR is for squamous cell cancer and adenocarcinoma combined.

Citation	Population	Time Period	RR or OR Unadjusted for Cigts./Day	RR or OR Adjusted for Cigts./Day	Remarks
Jöckel, K.-H. et al., *Int J. Epidemiol.*, 21: 202-213, 1992	Case-control study of 194 lung cancer patients, 194 hospital controls, and 194 population controls in five German cities	Not stated	0.31 (M) 95% CI, 0.17-0.56	0.41 (M) 95% CI, 0.21-0.81	Unadjusted OR is calculated from the data provided by the authors. The OR adjusted for cigarettes per day is also adjusted for years since quitting.

Table 1B
Epidemiological Studies of Filter Cigarettes vs. Non-Filter Cigarettes for Lung Cancer
Citations Primarily Taken from P. N. Lee (2001)

Citation	Population	Time Period	RR or OR Unadjusted for Cigts./Day	RR or OR Adjusted for Cigts./Day	Remarks
Doll, R., and Bradford Hill, A., *Brit. Med. J.*, 2: 1271-1286, 1952	Case-control study of 1465 UK lung cancer cases and 1465 matched hospital controls	1948-1952	0.18 (M) 95% CI, 0.05-0.63		The OR has been calculated from the numbers of cases and controls, and no factors have been adjusted for. The number of cases who smoked filter cigarettes was very small (3).
Wicken, A. J., *Environmental and personal factors in lung cancer and bronchitis mortality in Northern Ireland, 1960-1962*, Tobacco Research Council, 1966	Case-control study of 803 male and 151 female UK lung cancer cases and 551 male and 30 female matched controls	1960-1962	0.97 (M) 95% CI, 0.50-1.86 3.12 (F) 95% CI, 0.65-15.00		Results are unadjusted for any factor.
Segi, M., et al., *Lung Cancer*, 19: 157-165, 1979 (article in Japanese)[a]	Case control study of 378 male Japanese lung cancer patients and 756 matched controls	1962-1970	0.62 (M) 95% CI, 0.45-0.85		OR, adjusted for age, and 95% confidence limits were calculated from data provided by the authors.
Reid, D. D., taken from data reported in Lee, P. N., and Garfinkel, L., *J. Epidemiol. Community Health*, 35: 16-22, 1981	12.4-year prospective follow-up of 10,063 subjects aged 35-69 from a random sample of the population in Great Britain	1965-1977	1.01 (M) 95% CI, 0.69-1.48 0.92 (F) 95% CI, 0.39-2.16	1.17 (M) 95% CI, 0.79-1.72 1.01 (F) 95% CI, 0.43-2.37	RRs adjusted for cigarettes per day are also adjusted for age.

Citation	Population	Time Period	RR or OR Unadjusted for Cigts./Day	RR or OR Adjusted for Cigts./Day	Remarks
Dean, G., et al., *Report on a Second Retrospective Mortality Study in North-East England – Part 1. Factors Related to Mortality from Lung Cancer, Bronchitis, Heart Disease and Stroke in Cleveland County, with Particular Emphasis on the Relative Risks Associated with Smoking Filter and Plain Cigarettes.* (Research Paper 14), London	Case-control study of 616 deceased male and 150 deceased female lung cancer cases and 2,563 male and 2,958 female population controls from Cleveland County, UK	1969-1972	0.32 (M) 95% CI, 0.19-0.54 0.31 (F) 95% CI, 0.16-0.62	0.35 (M) 95% CI, 0.21-0.59 0.32 (F) 95% CI, 0.16-0.64	The OR unadjusted for cigarettes per day is adjusted for age. The adjusted OR is adjusted for both age and cigarettes per day.
Hirayama, T., *Lung cancer: Causes and prevention. Proceedings of the International Lung Cancer Update Conference, held in New Orleans, Louisiana, March 3-5, 1983, eds. M. Mizell and P. Correa, pp. 175-195. New York: Verlag Chemie International, 1984*	Prospective study of 256,118 adults aged 40 years and above in Japan	1966-1981		0.51	No information is provided regarding adjustment factors. The conservative viewpoint has been taken that this number represents the RR adjusted for cigarettes per day. In that this result has no associated confidence limits, it cannot be included in the meta-analysis.
Ockene, J. K., et al., *Amer. J. Public Health*, 80: 954-958, 1990	Prospective study of 12,866 men enrolled in the Multiple Risk Factor Intervention Trial (MRFIT) in the US	1973-1985		0.53 (M) 95% CI, 0.24-1.17	RR calculated from regression coefficient. RR is adjusted for age, cigarettes per day, age at start, tar, nicotine, alcohol, blood pressure, cholesterol, and serum thiocyanate.

Citation	Population	Time Period	RR or OR Unadjusted for Cigts./Day	RR or OR Adjusted for Cigts./Day	Remarks
Ives, J. C., *Environmental exposures and lung cancer risk among women in Harris County, Texas, 1977-1980*, Thesis, 1984	Case-control study of 259 female lung cancer cases and 278 female population controls in Harris County, Texas	1977-1980	1.34 (F) 95% CI, 0.80-2.23		Both the ORs and the 95% confidence limits were calculated from the data contained in the thesis. ORs are not adjusted for any cofactor.
Correa, P., et al., *Lung cancer: Causes and Prevention*, eds. M. Mizell and P. Correa, pp. 73-82. New York: Verlag Chemie International, 1984	Case-control study of 1338 lung cancer cases and 1393 hospital controls in Louisiana	1979-1981	0.55 95% CI, 0.35-0.85		OR is adjusted for age and sex. ORs not provided separately for males and females.
Garfinkel, L., and Stellman, S. D., *J. Cancer Res.*, 48: 6951-6955, 1988	Prospective study of a cohort of 619,225 women in the US (CPS-II)	1982-1986		0.66 (F) 95% CI, 0.57-0.78	RR is adjusted for age as well as for cigarettes per day. This study reports results on tar levels that are presented in Table 2B.
Thun, M. J., and Heath, C. W., Jr., *Preventive Medicine*, 26: 422-426, 1997	Prospective study of a cohort of 700,000 individuals (220,000 current smokers and 480,000 lifetime non-smokers) in the US (CPS-II)	1982-1989	0.47 (M) 0.51 (F)		RRs are estimated from data in graph form. The values given are adjusted for age. Since these are simply estimates based on graphed data, and since they would have considerable weight, they are not included in the meta-analysis.
Choi, S.-Y., et al., *Korean J. Epidemiol.*, 11: 66-80, 1989	Case-control study of 280 male lung cancer cases and 560 male hospital controls in Korea	1985-1988	0.06 (M) 95% CI, 0.01-0.30		OR is unadjusted for any factor.

Citation	Population	Time Period	RR or OR Unadjusted for Cigts./Day	RR or OR Adjusted for Cigts./Day	Remarks
Sobue, T., et al., *Japanese J. Cancer Res.*, 85: 464-473, 1994[a]	Case-control study of 1082 male lung cancer cases and 1141 hospital controls in Japan	1986-1988	0.55 (M) 95% CI, 0.34-0.90	0.67 (M) 95% CI, 0.38-1.11	Unadjusted OR and 95% confidence limits are calculated from data provided by the authors. OR, adjusted for cigarettes per day, is also adjusted for age, smoking duration, fraction of cigarette smoked and depth of inhalation.
Wakai, K., et al., *J. Epidemiol.*, 7: 99-105, 1997	Case-control study of 333 male Japanese lung cancer cases and 666 male controls matched on the basis of age and residence	1988-1991	1.16 (M) 95% CI, 0.31-3.33	1.02 (M) 95% CI, 0.51-1.05	Unadjusted OR is calculated from data provided by the authors. OR adjusted for cigarettes per day is also adjusted for age, age started to smoke, fraction of cigarette smoked, and depth of inhalation.
Simonato, L., et al., *Int. J. Cancer*, 91: 876-887, 2001[a]	Combination of 10 European case-control studies; filter-non-filter comparisons were based on 8 centers with 3562 male lung cancer cases and 2979 male matched controls, and 860 female cases and 600 matched controls	1988-1994	0.92 (M) 95% CI, 0.76-1.10 0.49 (F) 95% CI, 0.32-0.75		ORs represent comparison of lifetime filter only to lifetime non-filter only. ORs and 95% confidence limits were calculated from data provided by the authors. ORs are adjusted for age, education, and study center.
De Stefani, E., et al., *Cancer Epidemiol., Biomarkers & Prevention*, 5: 679-682, 1996	Case-control study of 320 lung cancer cases (307 men and 13 women) and 320 matched hospital controls in Uruguay	1994-1995	0.73 (M) 95% CI, 0.51-1.05		OR is adjusted for age, residence, urban/rural, education, body mass index, and family history of lung cancer.

Citation	Population	Time Period	RR or OR Unadjusted for Cigts./Day	RR or OR Adjusted for Cigts./Day	Remarks
Zemla, B., et al., *Neoplasma*, 35: 135-143, 1988	Case-control study of 210 male lung cancer cases and 420 matched hospital controls in Poland	Not stated	0.97 (M)		OR is not adjusted for any cofactors. There are no confidence limits provided, therefore, this result is not included in the meta-analysis.

a. Not included in P. N. Lee (2001).

Table 2A
Epidemiological Studies of Low-Tar Cigarettes vs. High-Tar Cigarettes for Lung Cancer
Citations Taken from Monograph No. 13

Citation	Population	Time Period	RR or OR Unadjusted for Cigts./Day	RR or OR Adjusted for Cigts./Day	Remarks
Hammond, E. C., et al., Cold Spring Harbor Conferences on Cell Proliferation, Volume 4. *Origins of Human Cancer*, Book A, *Incidence of Cancer in Humans*, pp. 101-112, 1977	12-year follow-up of CPS-I, a prospective mortality study of over 1 million men and women	1960-1972			This study reports on exactly the same study as cited below (Hammond, *Environ. Res.*) and cites exactly the same results.
Hammond, E. C., et al., *Environ. Res.*, 12: 263-274, 1976	12-year follow-up of CPS-I, a prospective mortality study of over 1 million men and women	1960-1972		1960-1966 0.83 (M) 95% CI, 0.64-1.08 0.57 (F) 95% CI, 0.36-0.91 1966-1972 0.79 (M) 95% CI, 0.58-1.08 0.62 (F) 95% CI, 0.41-0.94	RRs compare low-tar (<17.6 mg/cigarette) smokers to high-tar (25.8-35.7 mg/cigarette) smokers. In addition to adjustment for cigarettes per day, RRs are adjusted for age, race,, age at start, urban/rural, occupation, education, history of lung cancer, and history of CHD. It should be noted that the RRs cited in Monograph 13 refer to coronary heart disease and not lung cancer.

Citation	Population	Time Period	RR or OR Unadjusted for Cigts./Day	RR or OR Adjusted for Cigts./Day	Remarks
Higgenbottam, T., et al., *J. Epidemiol. Community Health*, 36: 113-117, 1982	10-year follow-up of 17, 475 male civil servants, aged 40-64, and a sample of male British residents	1965-1975		0.56 (M) 95% CI, 0.36-0.86	RR compares low-tar (18-23 mg tar/cigarette) to high-tar (>33 mg cigarette). RR is adjusted for age, cigarettes per day, inhalation, and employment grade. RR is calculated from individual values for cigarettes per day groupings and inhalers and non-inhalers. Contrary to Monograph 13, the result is statistically significant (95% CI, 0.36-0.86).
Borland, C., et al., *BMJ*, 287: 1583-1586, 1983	Prospective 10-year follow-up of the Whitehall study involving 4,910 male smokers of cigarettes with known CO yields (same population is Higgenbottom above)	1967-1979			Although this study cites a RR of 0.67 for smokers of "high" CO cigarettes compared to smokers of "low" CO cigarettes, this RR cannot be used in a meta-analysis comparing high-tar to low-tar. This is because, as the authors point out, the observed correlation between CO and tar delivery in their sample was a statistically non-significant R = 0.5.
Tang, J.-L., et al., *BMJ*, 311: 1530-1533, 1995	Four prospective mortality studies from the United Kingdom	1967-1982		0.75 (M) 95% CI, 0.52-1.09	This paper compares two groups of smokers, low-tar and high-tar, differing by 15 mg tar/cigarette. The RR is adjusted for age, cigarettes per day, and study.

Citation	Population	Time Period	RR or OR Unadjusted for Cigts./Day	RR or OR Adjusted for Cigts./Day	Remarks
Augustine, A., et al., *Amer. J. Public Health*, 79: 188-191, 1989	Case-control study of 1,242 lung cancer cases and 2,300 sex- and age-matched hospital controls	1969-1984			This study compares neither filter/non-filter nor low-tar/high-tar. The referent group consists of smokers who switched to a lower tar cigarette without increasing cigts/ day. ORs are calculated for switchers who increase either 1-10 or 21+ cigts/day
Kuller, L. H., et al., *Preventive Med.*, 20: 638-654, 1991	10.5-year follow-up of the MRFIT participants	1972-1985	0.73 (M) 95% CI, 0.38-1.41	0.88 (M) 95% CI, 0.52-1.49	This study compares smokers of low-tar (<15 mg/cigarette) to smokers of high-tar (>20 mg/cigarette) cigarettes. Unadjusted RR is calculated from data presented in the citation. RR adjusted for cigarettes per day is also adjusted for age, cholesterol, and blood pressure. Tabulation of RR data in Monograph 13 is incomplete. Only partial information for smokers of high nicotine (>1.5 mg/cigarette) compared to low nicotine (<1.0 mg/cigarette) is presented. The adjusted RR for this comparison is 0.68, and the calculated unadjusted RR is 0.62.

Citation	Population	Time Period	RR or OR Unadjusted for Cigts./Day	RR or OR Adjusted for Cigts./Day	Remarks
Lubin, J. H:, et al., *Int. J. Cancer*, 33: 569-576, 1984	A case-control study of 7,804 cases and 15,207 hospital-based controls in seven Western European locations	1976-1980	0.98 (M) 95% CI, 0.75-1.28 0.66 (F) 95% CI, 0.37-1.16	0.71 (M) 95% CI, 0.55-0.93 0.67 (F) 95% CI, 0.38-1.18	This study compares smokers of low-tar (15.6 mg) cigarettes to smokers of high-tar (29.8 mg for males and 25.7 mg for females) cigarettes. Unadjusted ORs were calculated from data provided in the citation. ORs adjusted for cigarettes per day also adjusted for duration of smoking and, for ex-smokers, years since quit.
Benhamou, S., et al., *Int. J. Epidemiol.*, 23: 437-443, 1994	Case-control study of 1,114 lung cancer patients and 1,466 hospital controls	1976-1980	0.26 (M) 95% CI, 0.14-0.48	0.30 (M) 95% CI, 0.10-0.91	This study compares smokers of "light imported cigarettes" (tar level unknown) with smokers of high-tar (>30 mg) cigarettes for at least 75% of their smoking career. The OR unadjusted for cigarettes per day is adjusted for age. The OR adjusted for cigarettes per day is also adjusted for age and smoking duration.
Vutuc, C., and Kunze, M., *Preventive Medicine*, 11: 713-716, 1982	Case-control study of 297 female lung cancers and 580 half hospital and half neighborhood controls from 15 lung cancer centers in Austria	1976-1980	0.32 (F) 95% CI, 0.09-1.17	0.29 (F) 95% CI, 0.09-0.95	This study compares smokers of low-tar (<15 mg) cigarettes who smoked such cigarettes through most of their smoking history to smokers of high-tar (>24 mg) cigarettes. The unadjusted OR is calculated from numbers of cases and controls in the citation. OR adjusted for cigarettes per day is also adjusted for age and years of smoking.

Citation	Population	Time Period	RR or OR Unadjusted for Cigts./Day	RR or OR Adjusted for Cigts./Day	Remarks
Vutuc, C., and Kunze, M., *J. Natl. Cancer Inst.*, 71: 435-437, 1983	Case control study of 252 male lung cancers and 839 half hospital and half neighborhood controls from 15 lung cancer centers in Austria	1976-1980	0.32 (M) 95% CI, 0.09-1.08	0.30 (M) 95% CI, 0.11-0.81	This study compares smokers of low-tar (<15 mg) cigarettes who smoked such cigarettes through most of their smoking history to smokers of high-tar (>24 mg) cigarettes. The unadjusted OR is calculated from numbers of cases and controls in the citation. OR adjusted for cigarettes per day is also adjusted for age and years of smoking.
Gillis, C. R., et al., *J. Epidemiol. Community Health*, 42: 38-43, 1988	Case-control study of 656 male lung cancer patients and 1,312 age-matched hospital controls	1977-1981	0.73 (M) 95% CI, 0.52-1.01	0.74 (M) 95% CI, 0.53-1.03	This study compares smokers of low/medium-tar (<17 mg/cigarette) cigarettes, medium-tar (17-22 mg/cigarette) cigarettes, medium/high-tar (23-28 mg/cigarette) cigarettes, high-tar (>28 mg/cigarette) cigarettes. The unadjusted OR compares smokers of cigarettes with 22 or less mg tar to smokers of cigarettes with 23 or more mg tar and is calculated from numbers of cases and controls in the citation. The OR adjusted for cigarettes per day compares the same two sets of smokers. It has not been adjusted for any other cofactors.

Citation	Population	Time Period	RR or OR Unadjusted for Cigts./Day	RR or OR Adjusted for Cigts./Day	Remarks
Alderson, M. R., et al., *J. Epidemiol. Community Health*, 39: 286-293, 1985	Case-control study of 12,693 in-patients	1977-1982		0.83 (M) 95% CI, 0.55-1.24 1.12 (F) 95% CI, 0.74-1.70	This study compares smokers of low-tar (<23 mg) cigarettes to smokers of high-tar (>28 mg) cigarettes. ORs were calculated by one of the authors of the study (P. N. Lee) and are published in a report to the Tobacco Manufacturers Association. ORs adjusted for cigarettes per day are also adjusted for age.
Wynder, E. L., and Kabat, G. C., *Cancer*, 62: 1223-1230, 1988	Case-control study of 1,278 Kreyberg I patients and 2,408 hospital controls and 807 Kreyberg II patents and 1,543 matched controls	1977-1984	1.32 (M) 95% CI, 0.89-1.95 0.93 (F) 95% CI, 0.61-1.42		This study compares smokers of low-tar (<10 mg/cigarette) cigarettes with smokers of high-tar (>15 mg/cigarette) cigarettes. The unadjusted ORs are calculated from numbers of cases and controls provided in the citation, and are not adjusted for any cofactor.
Petitti, D. B., and Friedman, G. D., *J. Chron. Dis.*, 38: 581-588, 1985	4-year prospective follow-up of 16,270 current regular smokers and 42,113 subjects who never used any form of tobacco	1979-1982			This is an intermediate report on the Kaiser Permanente study. Results are covered in the Sidney reference below that reports on a larger group with more years of follow-up.

Citation	Population	Time Period	RR or OR Unadjusted for Cigts./Day	RR or OR Adjusted for Cigts./Day	Remarks
Sidney, S., et al., *Cancer Causes and Control*, 4: 3-10, 1993	Prospective follow-up of 79,946 Kaiser Permanente Medical Care group members for an average of 5.6 years	1979-1985	0.92 (M) 95% CI, 0.48-1.73 1.49 (F) 95% CI, 0.78-2.87	0.79 (M) 95% CI, 0.41-1.50 1.49 (F) 95% CI, 0.76-2.94	This study compared smokers of low-tar (<11 mg/cigarette) cigarettes to smokers of high-tar (>18 mg/cigarette) cigarettes. RRs unadjusted for cigarettes per day are adjusted for age. RRs adjusted for cigarettes per day are also adjusted for age, race, education, and number of years smoking.
Wilcox, H. G., et al., *Preventive Med.*, 17: 263-272, 1988	Case-control study of all incident cases of lung cancer (763) in six areas of New Jersey and 900 population-based controls	1980-1981	0.53 (M) 95% CI, 0.29-0.97	0.61 (M) 95% CI, 0.32-1.13	This study compares smokers of low-tar (<14.0 mg/cigarette) cigarettes to smokers of high-tar (> 21.1-28 mg/cigarette) cigarettes. OR adjusted for cigarettes per day is also adjusted for smoking duration. The results described in Monograph 13 do not compare the ORs for the highest and lowest tar smokers.

Citation	Population	Time Period	RR or OR Unadjusted for Cigts./Day	RR or OR Adjusted for Cigts./Day	Remarks
Kaufman, D. W., et al., *Am. J. Epidemiol.*, 129: 703-711, 1989	Case-control study of 881 lung cancers and 2,570 hospital controls	1981-1986	0.11 (M) 95% CI, 0.04-0.30 0.17 (F) 95% CI, 0.07-0.43	0.25 (M) 95% CI, 0.08-0.82 0.21 (F) 95% CI, 0.05-0.93	This study compares smokers of low-tar (<22 mg/cigarette) cigarettes to smokers of high-tar (>29 mg/cigarette) cigarettes who smoked the same brand (or same tar level) for at least 10 years before hospital admission. ORs unadjusted for cigarettes per day were calculated from data provided in the citation and are not adjusted for any factor. ORs adjusted for cigarettes per day are also adjusted for age, race, age at start, religion, education, and year of interview. The results described in Monograph 13 refer to the entire group of smokers of the two tar levels, as opposed to those smoking the same tar level for at least 10 years. Moreover, the data are not stated in an obvious manner. The OR of 3.1 for smokers of the highest tar should be stated as an OR of 0.32 for smokers of the lowest tar level.

Table 2B
Epidemiological Studies of High-Tar Cigarettes vs. Low-Tar Cigarettes for Lung Cancer
Citations Taken from P. N. Lee (2001)

Citation	Population	Time Period	RR or OR Unadjusted for Cigts./Day	RR or OR Adjusted for Cigts./Day	Remarks
Speizer, F. E., et al., *Cancer Causes and Control*, 10: 475-482, 1999	16-year follow-up of 121,700 women (Nurse's Health Study)	1976-1992	0.50 (F) 95% CI, 0.36-0.67	1.00 (F) 95% CI, 0.71-1.43	This study compared smokers of the lowest tar tertile to the highest tar tertile. Specific tar levels were not specified. Both RRs were additionally adjusted for age and for age of start.
Garfinkel, L., and Stellman, S. D., *Cancer Res.*, 48: 6951-6955, 1988	Prospective study of a cohort of 619,225 women in the US (CPS-II)	1982-1986		0.63 (F)	This publication used a logistic regression model in which the tar yield of the cigarette currently smoked was a continuous variable together with the following categorical variables: age (5-yr group); number of cigarettes smoked per day, and inhalation (none, slight, moderate, deep). The RR shown here is application of this model to smokers of cigarettes of 5 mg tar yield compared to smokers of 20 mg tar yield. Confidence limits cannot be calculated for this RR, therefore it is not used in the meta-analysis. It should be noted that this publication draws on early data from CPS-II.

The data in Tables 1 and 2 were subjected to meta-analysis. A meta-analysis is a statistical technique that is used to combine large numbers of epidemiological studies in order to provide a single, or pooled, relative risk. Generally two types of techniques are used; namely, fixed effects meta-analysis and random effects meta-analysis. Fixed effects meta-analysis is based on the assumption that all the studies being comgined provide estimates of the same underlying risk. Random effects meta-analysis, on the other hand, assumes that each individual is estimating its own, unknown, true effect, which may vary about an overall mean. In both methods of analysis, large studies give a greater weight than small studies to the final estimate, but whereas fixed effects meta-analysis only takes within-study variation into account, the weighting in random effects meta-analysis depends also on the between-study variation. Views differ on which is the more appropriate technique. The following meta-analyses were carried out:

1. Meta-analysis of all RRs (or ORs) unadjusted for cigarettes per day from Tables 1A and 1B combined (filter vs. non-filter).
2. Meta-analysis of all RRs (or ORs) unadjusted for cigarettes per day from Table 1A (filter vs. non-filter).
3. Meta-analysis of all RRs (or ORs) adjusted for cigarettes per day from Table 1A and 1B combined (filter vs. non-filter).
4. Meta-analysis of all RRs (or ORs) adjusted for cigarettes per day from Table 1A (filter vs. non-filter).
5. Meta-analysis of all RRs (or ORs) unadjusted for cigarettes per day from Tables 2A and 2B combined (low-tar vs. high-tar).
6. Meta-analysis of all RRs (or ORs) unadjusted for cigarettes per day from Table 2A (low-tar vs. high tar).
7. Meta-analysis of all RRs (or ORs) adjusted for cigarettes per day from Tables 2A and 2B combined (low-tar vs. high-tar).
8. Meta-analysis of all RRs (or ORs) adjusted for cigarettes per day from Table 2A (low-tar vs. high-tar).

Analyzing the data in this manner will allow the following questions to be addressed.

1. Do the epidemiological studies that have compared smokers of filter vs. non-filter cigarettes or high-tar vs. low-tar cigarettes support the hypothesis that smokers of cigarettes with lower machine-measured tar yields are at lower risk for lung cancer?
2. Is any observed lowering of risk for lung cancer for smokers of cigarettes with lower machine-measured tar yields the consequence of adjusting the data for cigarettes per day; that is, when no such adjustments are made, does one continue to observe a decrease in risk?
3. Does inclusion of studies referenced by Lee (2001) change the results obtained when only studies included by Burns, et al., are pooled?

The results of these eight meta-analyses are tabulated in Table 3. These results provide answers to all three questions above. First, the results clearly demonstrate a statistically significant decrease in risk when either smokers of filter cigarettes are compared to smokers of non-filter cigarettes or when smokers of lower-tar cigarettes are compared to smokers of higher-tar cigarettes. Secondly, there is no significant difference between relative risks when comparison is made between pooling relative risks adjusted for cigarettes per day and pooling relative risks unadjusted for cigarettes per day. Lastly, inclusion of the additional studies cited in Lee (2001) does not change the results of the meta-analysis, although it of course does narrow the 95% confidence limits. These results clearly demonstrate that the hypothesis of Burns, et al., that any observed reduction in lung cancer risk for smokers of reduced machine-measured tar yields disappears when examining the risk to the smoker and not the risk on a per cigarette basis, is completely incorrect. Essentially equivalent reduction in risk is observed in either case – for the smoker irrespective of number of cigarettes per day, or on a per cigarette a day basis. We will see in a further section that this result is actually not at all unexpected based on data presented by Burns, et al., themselves.

Table 3 Pooled Relative Risks Comparing Filter vs. non-Filter or Low-Tar vs. High-tar for Lung Cancer Obtained by Meta-Analysis		
Sample	**Fixed Effects Meta-Analytic Relative Risk**	**Random Effects Meta-Analytic Relative Risk**
Table 1A and 1B, unadjusted (N=42)	0.64 (95% CI, 0.61-0.69)	0.61 (95% CI, 0.54-0.70)
Table 1A, unadjusted (N=26)	0.61 (95% CI, 0.56-0.65)	0.59 (95% CI, 0.51-0.69)
Table 1A and 1B, adjusted (N=33)	0.65 (95% CI, 0.61-0.70)	0.67 (95% CI, 0.58-0.76)
Table 1A, adjusted (N=25)	0.65 (95% CI, 0.60-0.70)	0.67 (95% CI, 0.57-0.79)
Table 2A and 2B, unadjusted (N=15)	0.72 (95% CI, 0.64-0.81)	0.60 (95% CI, 0.45-0.81)
Table 2A, unadjusted (N=14)	0.77 (95% CI, 0.67-0.88)	0.61 (95% CI, 0.44-0.84)
Table 2A and 2B, adjusted (N=21)	0.75 (95% CI, 0.68-0.83)	0.73 (95% CI, 0.64-0.83)
Table 2A, adjusted (N=20)	0.73 (95% CI, 0.66-0.81)	0.732 (95% CI, 0.63-0.82)

There is one other point that needs to be made regarding adjustment for cigarettes per day. Although not explicitly discussed in Chapter 4, the possibility exists that filter (low-tar) smokers could actually smoke fewer cigarettes per day. Therefore, if no adjustment were made for cigarettes per day, the finding of a lower relative risk (or odds ratio) for filter (low-tar) cigarettes could be the result not of a reduction in risk stemming from the cigarettes themselves but rather the result of fewer cigarettes being smoked. It is extremely important to note that the fact that essentially no difference was observed for the meta-analytic relative risk whether or not adjustment was made for cigarettes per day indicates that the result cannot be attributed to filter (low-tar) smokers consuming fewer cigarettes per day.

Although the meta-analytic relative risk for lung cancer associated with filter cigarette (low-tar) smokers compared to non-filter cigarette (high-tar) smokers, based on 83 data points, shows a clear, statistically significant advantage for smokers of cigarettes with lower machine-measured yields (assuming that it is reasonable to assume that filter cigarettes at any given time have a lower machine-measured yield than non-filter cigarettes), the reduction in risk is within the range considered to be weak. This can be seen more easily if one looks at the reciprocal of the pooled relative risk. For example the pooled RR (fixed effects) for smokers of filter cigarettes compared to non-filter cigarettes, unadjusted for cigarettes per day, is 0.64 (entry 1 in Table 3). If one instead compares the pooled RR for smokers of non-filter cigarettes compared to smokers of filter cigarettes, the result would be the reciprocal of 0.64, or 1.56. Since this RR is less than 2, it is possible that the result could be explicable by other factors such as confounding (Breslow and Day, 1980). Burns, et al., have already referred to confounding as a possible explanation for the observation of reduced lung cancer risk in smokers of lower-delivery cigarettes, although, as has been noted, no supporting data have been presented. A technique that is frequently used by epidemiologists to assess the likelihood of a weak association being causal is the application of the Bradford Hill "aspects of an association" (Bradford Hill, 1965). The Bradford Hill aspects that

assume the greatest importance for assessing potential causality of the association of cigarette tar reduction with reduction in lung cancer risk are the strength of the association, consistency of the association, dose-response (biological gradient), and biological plausibility (analogy).

The strength of the association was discussed in the previous paragraph, and to summarize, although the meta-analytical result is statistically significant, the association is weak. There are a number of publications, cited in Tables 2A and 2B, dealing with the relationship of tar level and lung cancer relative risk, that provide data on dose-response. These results are summarized in Table 4. Inspection of Table 4 shows that with the exception of two results out of 12 (smokers of cigarettes with 20 mg tar or greater from Higgenbottam, et al., and female smokers from Sidney, et al.) there is an excellent dose-response relationship between tar level and risk of lung cancer observed. Also, the publication by Garfinkel and Stellman (1988) should be noted. These authors used CPS-II data after four years of follow-up to derive a relationship between tar content and lung cancer risk in women. Their relationship predicted a RR risk of lung cancer for smokers of cigarettes with FTC yields of 15, 10, and 5 mg tar of 0.86, 0.74, and 0.63 compared to the reference group of women smoking cigarettes with a machine-measured delivery of 20 mg tar. Even the limited data available strongly support a dose-response relationship between tar delivery and lung cancer risk.

As can be seen from the notes to Table 4, most of the studies adjusted the RRs (or ORs) for cigarettes per day. As a consequence, the point can be made, as was made by the authors of Chapter 4 regarding the individual study point estimates themselves, that had the results not been adjusted for cigarettes per day, no dose-response would have been observed. There is insufficient data presented in the seven studies noted in Table 4 to attempt to compare the dose-response curves based on data both adjusted and unadjusted for cigarettes per day, as was done for many of the point estimates. However, the fact that adjustment for cigarettes per day had little to no effect on the pooled RRs for the point estimates themselves provides some confidence that adjustment for cigarettes per day would have little to no effect on the observed dose-response relationships.

It is clear that it is biologically plausible that smokers of reduced tar cigarettes, as determined by machine smoking, would be at lower risk for lung cancer than smokers of higher tar cigarettes. As was pointed out earlier in Chapter 4, it is logical to assume that reduction of tar would translate into a reduction of risk for lung cancer. Virtually every epidemiological study that has investigated the relationship of lung cancer associated with cigarette smoking as a function of cigarettes per day has found a strong dose-response relationship. This dose-response relationship has been codified into the well known Doll, Peto equation relating absolute risk of lung cancer to daily cigarette consumption and smoking duration that is discussed briefly in Section Q. Only under circumstances where smokers of lower delivery cigarettes compensated fully would one not expect to see a decrease in lung cancer risk as a function of cigarette tar yield. The epidemiological data that was presented in Chapter 4 and analyzed fully above strongly suggests that full compensation does not occur. As a consequence, it is clear that the observed reduction in risk is biologically plausible.

The last Bradford Hill aspect to be discussed is consistency. Certainly, simple inspection of the results suggests that they are consistent. Of the 83 estimates for the filter/non-filter comparison, 69 are less than 1.00, with 35 statistically significant reductions at $p<0.05$. None of the 15 estimates greater than 1.00 are statistically significant. Of the 37 estimates for the low-tar/high-tar comparison, 32 are less than 1.00, 1 is equal to 1.00, and 4 are greater than 1.00. Fourteen of the decreases and none of the increases are statistically significant at $p<0.05$.

If one carries out an analysis of heterogeneity, however, it is clear that three of the four comparisons are statistically heterogeneous. For the filter/non-filter comparison, unadjusted for cigarettes per day, $\chi^2 = 139.02$ on 41 df ($p<0.001$); for the filter/non-filter comparison, adjusted for

Table 4 Relative Risk for Lung Cancer as a Function of Relative Tar Yield					
Citation	**Relative Risk at**				
	Highest Tar				**Lowest Tar**
Hammond, E. C., et al., *Environ. Res.*, 12: 263-274, 1976 (CPS-I)[a]	1.00 (M) 1.00 (F)	0.95 (M) 0.79 (F)	0.81 (M) 0.60 (F)		
Higgenbottam, T., et al., *J. Epidemiol. Community Health*, 36: 113-117, 1982[b]	1.00 (M)[c] 1.00 (M)[d] 1.00 (M)[e]	0.33 (M)[c] 0.59 (M)[d] 1.12 (M)[e]	0.24 (M)[c] 0.56 (M)[d] 1.25 (M)[e]		
Kuller, L. H., et al., *Preventive Med.*, 20: 638-654, 1991[f]	1.00 (M)	0.71 (M)	0.88 (M)		
Lubin, J. H:, et al., *Int. J. Cancer*, 33: 569-576, 1984[g]	1.00 (M) 1.00 (F)	0.93 (M) 0.73 (F)	0.93 (M) 0.87 (F)	1.21 (M) 1.27 (F)	0.71 (M) 0.67 (F)
Vutuc, C., and Kunze, M., *Preventive Medicine*, 11: 713-716, 1982[h]	1.00 (F)	0.43 (F)	0.24 (F)		
Vutuc, C., and Kunze, M., *J. Natl. Cancer Inst.*, 71: 435-437, 1983[i]	1.00 (M)	0.56 (M)	0.30 (M)		
Sidney, S., et al., *Cancer Causes and Control*, 4: 3-10, 1993[j]	1.00 (M) 1.00 (F)	1.02 (M) 1.39 (F)	0.79 (M) 1.49 (F)		
Kaufman, D. W., et al., *Am. J. Epidemiol.*, 129: 703-711, 1989[k]	1.00 (M) 1.00 (F)	0.98 (M) 0.38 (F)	0.25 (M) 0.21 (F)		

a. Comparison of matched groups, matching being based on age, cigarettes/day, age of start, place of residence, occupational exposure, education, history of lung cancer, and history of heart disease
b. Data for inhalers only; RR adjusted for age and employment grade
c. Smokers of 1-9 cigarettes/day
d. Smokers of 10-19 cigarettes/day
e. Smokers of 20+ cigarettes/day
f. Adjusted for age, serum cholesterol, diastolic blood pressure, and cigarettes/day
g. Test of linear trend, $p<0.01$
h. Adjusted for age, smoking duration, and cigarettes/day
i. Data for smokers whose main brands were in these tar groupings; adjusted for age, smoking duration, and cigarettes/day
j. Adjusted for age, race, education, smoking duration, and cigarettes/day
k. Based on tar content of cigarettes smoked 10 years before admission to hospital; adjusted for age, sex, ethnic group, geographic region, education, year of interview, age at start of smoking and cigarettes/day

cigarettes per day, χ^2 = 96.61 on32 df (p<0.001); and for the low-tar/high-tar comparison, unadjusted for cigarettes per day, χ^2 = 64.18 on14 df (p<0.001). Only the result for the low-tar/high-tar comparison, adjusted for cigarettes per day did not show significant heterogeneity at the 95% level (χ^2 = 30.76 on 20 df, p<0.1). Although a number of studies contributed to the observed heterogeneity, no single study was identified the removal of which would have significantly reduced heterogeneity. In that there was overlap among a number of the studies, those studies that were identified as overlapping considerably with other studies were removed from the filter/non-filter sample. The studies removed were Wynder and Stellman (1979), Hawthorne (1983), Benhamou, E. (1987), Jöckel (1992), Benhamou, S. (1994), and Agudo (1994). Removal of these studies reduced heterogeneity only slightly (χ^2 = 121.05, on 35 df for filter/non-filter (p<0.001) unadjusted for cigarettes per day, and χ^2 = 90.90 on 26 df for filter/non-filter (p<0.001) adjusted for cigarettes per day). A number of factors were identified that contributed to the heterogeneity. These factors, and their influence on the pooled RRs (fixed effects) for the filter/non-filter comparison after elimination of overlapping studies are shown in Table 5.

Examination of the results of Table 5 would indicate that with two exceptions optimum conduct of an epidemiological study comparing the risk of lung cancer for smokers of filter cigarettes to smokers of non-filter cigarettes would lead to even a more marked decrease in risk of lung cancer. The pooled RRs for larger studies compared to smaller studies show a decrease in lung cancer risk. Studies where full histological confirmation of lung cancer was carried out show a marked decrease in pooled RRs. Studies that compared lifetime smokers of filter cigarettes to lifetime smokers of non-filter cigarettes showed a very marked decrease for adjusted RRs compared to studies where the comparison was made at an arbitrary time point. The difference for unadjusted RRs was not significantly affected. On the other hand pooled RRs for prospective studies were clearly increased compared to pooled RRs for case-control studies. It is a reasonable assumption that prospective studies are subject to fewer systematic biases than are case-control studies. Lastly, the differences observed for year of finish are quite difficult to interpret. Year of finish is often used as a surrogate for study quality, in that more recent studies are often of higher quality. As can be seen from Table 5, no obvious pattern emerges. It is interesting to note that neither failure to adjust for age or failure to adjust for other potential confounders had a significant effect on the pooled RRs. Therefore, although the pooled results of the meta-analyses comparing smokers of filter cigarettes to smokers of non-filter cigarettes with respect to risk of lung cancer demonstrate statistical heterogeneity, an analysis of that heterogeneity suggests that elimination of heterogeneity would most likely not have a strong effect on the pooled RRs and might even have resulted in a decrease in pooled RRs.

In conclusion it would appear that application of the Bradford-Hill aspects strongly support causality with respect to epidemiological studies that have investigated the effects of tar reduction, as determined by machine smoking, on lung cancer risk. Those studies that have investigated a dose-response relationship have generally confirmed such a relationship. The results are clearly biologically plausible. And, lastly, although the studies are statistically heterogeneous, identification of those factors that have contributed to the heterogeneity would suggest, in three cases out of four, that a homogeneous set of studies would have exhibited even a greater reduction in lung cancer risk.

Table 5
Factors Contributing to Statistical Heterogeneity in Filter/Non-Filter Comparisons (Based on Data in Tables 1A and 1B with Exclusions Mentioned Above)

Factor	Unadjusted for Cigts/Day			Adjusted for Cigts/Day		
	N	RR (95% CI)		N	RR (95% CI)	
Year of finish						
1952-80	14	0.65 (0.59-0.72)		9	0.54 (0.48-0.60)	
1981-90	11	0.57 (0.50-0.66)		11	0.74 (0.67-0.82)	
1990+	11	0.70 (0.63-0.79)	p<0.1	7	0.64 (0.52-0.78)	p<0.001
Number of lung cancers						
1-100	10	0.77 (0.63-0.95)		9	0.85 (0.70-1.03)	
101-300	12	0.57 (0.50-0.64)		9	0.48 (0.41-0.57)	
301+	14	0.67 (0.62-0.73)	p<0.05	9	0.67 (0.61-0.73)	p<0.001
Full histological confirmation						
Yes	11	0.57 (0.52-0.63)		9	0.51 (0.45-0.57)	
No	25	0.75 (0.68-0.82)	p<0.001	18	0.75 (0.68-0.82)	p<0.001
Study type						
Prospective	9	0.78 (0.64-0.94)		12	0.77 (0.69-0.85)	
Case-control	27	0.64 (0.59-0.68)	p<0.1	15	0.54 (0.49-0.60)	p<0.001
Filter/non-filter comparison						
F/NF one time point	16	0.69 (0.60-0.78)		12	0.82 (0.72-0.93)	
F only/NF only lifetime	9	0.73 (0.67-0.80)		6	0.59 (0.52-0.68)	
Other	11	0.50 (0.44-0.57)	p<0.001	9	0.57 (0.51-0.64)	p<0.001
Standardized for age						
Yes	14	0.65 (0.59-0.72)		23	0.63 (0.59-0.69)	
No	22	0.65 (0.60-0.71)	NS*	4	0.72 (0.58-0.90)	NS*
Standardized for other factors (confounding)						
Yes	6	0.68 (0.60-0.76)		13	0.71 (0.63-0.81)	
No	30	0.64 (0.59-0.69)	NS*	14	0.61 (0.56-0.67)	p<0.1

*NS: p>0.1

In that Burns, et al., did not make any attempt to analyze the data that they themselves tabulated in order to attempt to justify their hypothesis regarding the effect of cigarettes per day on the observed epidemiological relative risks, how do they attempt to justify their hypothesis? Support for their claim is made in a piecemeal fashion in the next several sections, and it is necessary to look at each point in some detail.

In this section several studies are discussed. The first study discussed was the earliest case-control study to have examined a comparison of the comparative risk for lung cancer in smokers of filter versus non-filter cigarettes; namely, the study conducted in the US by Bross and Gibson (1968). Burns, et al., point out that the relatively low OR obtained, that is, 0.59, was somewhat surprising given that this study was conducted very soon following the introduction of filtered cigarettes. This point is clearly well taken; however, it should be noted that by 1960 approximately one-half of American smokers were smoking filter cigarettes (Forey, et al., 2002). However, the attempt by Burns, et al., to explain this result by attributing it to the fact that the results were stratified on cigarettes per day is completely incorrect. First of all, as can be seen from the first entry in Table 1A, the same OR ratio is obtained whether or not the results are adjusted or unadjusted for cigarettes per day. Secondly, Burns attempts to justify his hypothesis by pointing out that the authors presented a table demonstrating that 38% of the filter smokers smoked more than one pack per day in contrast to 35% of non-filter smokers. Not only is the difference between 38% and 35% not statistically valid, this difference is too small to produce any material bias. Moreover, simply saying that more filter smokers smoke over a pack a day does not really say anything about the number of cigarettes per day smoked. One cannot possibly determine, for example, if the 38% filter smokers who smoked more than one pack a day smoked an average of 1.5 packs per day, while the 35% of non-filter smokers smoked an average of 2 packs per day.

It is likely that Bross and Gibson were able to observe a decrease in lung cancer risk for smokers of filter cigarettes, despite the relatively short time that filter cigarettes were on the market, because the case-control design allows the investigator to focus on that portion of the total sample that actually smoked filter cigarettes. Had Bross and Gibson attempted to calculate lung cancer risk for their total sample, and compare this risk to the lung cancer risk determined for a similar population in 1950, it is virtually certain that a significant difference would not have been observed.

The next study discussed in this section is the published results of 12 years of follow-up of the CPS-I population. This publication (Hammond, et al., 1976) compared smokers of low-yield (<17.6 mg tar) cigarettes to smokers of high-yield (>25.8 mg tar) cigarettes and found an approximately 20% decrease in risk for males and a 40% decrease in risk for females (see Table 2A). Burns, et al., point out that these results have been adjusted for cigarettes per day, and that the authors of the study cautioned that the risk differences between smokers of different yield cigarettes would disappear if smokers had increased the number of cigarettes smoked per day when they switched from high-tar to low-tar cigarettes. Hammond, et al., (1976) did not present data that could be used to calculate the unadjusted relative risk. However, such data were available to them. It would seem that instead of simply cautioning the scientific community regarding the potential role of adjusting for cigarettes per day that they could have actually carried out the necessary calculations and presented the results. We have carried out a very similar calculation on the first six years of follow up for CPS-I, wherein we have compared smokers of high-tar (25.8-35.7 mg tar) to smokers of low-tar (14.6-17.3 mg tar) both adjusted and unadjusted for cigarettes per day. The tar categories are not exactly the same as used by Hammond, et al.; however, they are close. The results are as follows:

Males – Low-tar vs. high-tar adjusted for cigarettes per day: RR = 0.71

Males – Low-tar vs. high-tar unadjusted for cigarettes per day: RR = 0.71

Females – Low-tar vs. high-tar adjusted for cigarettes per day: RR = 0.50

Females – Low-tar vs. high-tar unadjusted for cigarettes per day: RR = 0.46

These results are not exactly equivalent to those reported by Hammond, et al. (1976) for two reasons. One is that the tar level comparison is not identical. Secondly, Hammond, et al., adjusted for a number of other cofactors, which result in a slight increase in RR values. However, the results are clear – adjustment for cigarettes per day made no change in the relative risk for men, and actually resulted in a slight increase, not decrease, for women. Consequently, the decrease in lung cancer risk as a function of decrease in tar cannot be attributed to the fact that the data were adjusted for cigarettes per day.

The next study referred to in this section is one by Augustine, et al., (1989). These authors carried out a study in which they interviewed 781 male lung cancer cases and 1432 matched controls and 461 female lung cancer cases and 868 matched controls who had switched from smoking non-filter cigarettes to smoking filter cigarettes. They report an average increase of 5.9 cigarettes per day for male lung cancer cases, compared to an average increase of 3.9 cigarettes per day for male controls, and an average increase of 7.8 cigarettes per day for female lung cancer cases compared to an average increase of 4.7 cigarettes per day for female controls. They also demonstrate an increase in OR for cases who had increased the number of cigarettes per day compared to those who had not. Although this study is clearly of interest, it provides no information on the epidemiology of a comparison of the lung cancer risk for filter smokers compared to non-filter smokers, since no odds ratio for this comparison was presented or could be calculated from the data provided. The increased odds ratios for individuals who smoked a greater number of cigarettes per day, compared to those who did not is certainly not surprising. However, it is not relevant to the lung cancer risk for smokers of filter cigarettes compared to smokers of non-filter cigarettes, since it is quite possible that the increase in odds ratio resulting from an increase in cigarettes smoked per day would be less in most if not all cases than would have been obtained had these individuals not switched to filter cigarettes. It is clearly possible that individuals who switch to filter cigarettes will increase their average number of cigarettes per day. However, even if this is the case, the vast body of epidemiological studies summarized in Tables 1 and 2 strongly suggest that, even when results are not stratified on the basis of cigarettes per day, the lung cancer risk for smokers of lower-tar cigarettes, as determined by machine smoking, are at lower risk for lung cancer.

The rest of this section simply summarizes in a qualitative manner the remaining studies, although a study by Auerbach, et al. (1975) is mentioned that reports that histological changes in the airways of smokers have become less evident over the time period in which tar yields were declining.

Burns, et al., conclude this section with the following paragraph:

> "In summary, most case-control and prospective mortality studies conducted in different geographic locations demonstrated differences in lung cancer risks for filter and low-tar (machine measured) smokers compared with nonfilter and high-tar smokers when controlled for cigarettes smoked per day. The question that remains is whether differences in lung cancer experience are due to differences in machine-measured tar yield of the cigarettes smoked, due to differences in other characteristics of the smokers who use these products, or due to differences in model misspecification in these studies."

This concluding statement is not different from the concluding statement of the previous section. This is perhaps not surprising since, despite having presented a wealth of data, Burns, et al., failed to analyze these data. The analysis we have presented in this section strongly suggests that there

is no "model misspecification in these studies." That is, the epidemiological results are the same with or without adjustment for cigarettes per day.

G. New Analyses of the American Cancer Society's Cancer Prevention Study I Data

This section presents another piece of evidence that Burns, et al., claim as support of their hypothesis that the reduction in lung cancer risk associated with a reduction in machine-measured tar is an artifact of the epidemiology as opposed to being causal in nature. The introduction to this section states that a reexamination of the CPS-I data set was inconclusive as to whether compensatory changes in the number of cigarettes smoked per day when smokers switch to a lower nicotine cigarette introduce a bias sufficient to explain the observed increased lung cancer risk among smokers of high-yield cigarettes. This statement appears to be in conflict with data presented in Section F above based on the relative risks calculated as a function of tar level for the first six years of follow-up of CPS-I both adjusted and unadjusted for cigarettes per day. However, Burns, et al., base their conclusion on a survival analysis that examined lung cancer risks for smokers of different yield cigarettes using the yield of the most recent follow-up. This analysis "did not show a significant effect of tar for lung cancer risk with either cigarettes smoked per day at baseline or at the most recent follow-up used to control for intensity of smoking." The authors continue by pointing out, "[S]ince there was no effect of tar on lung cancer risk to examine, it was not possible to determine whether controlling for CPD using the number of cigarettes per day prior to switching brands reduced or eliminated the effect of tar on lung cancer risk." No details of this survival analysis are presented in Monograph 13. As a consequence, it is not possible to critique either the methodology or the results.

Since Burns, et al., claim that an unadjusted relative risk could not be calculated, they proceed to carry out the analysis that is represented graphically in Figure 4-5. The left-hand side of this graph represents the relative risk calculated after 12 years of follow up adjusted for cigarettes per day as a function of tar level. As can be seen there is an increasing relative risk for lung cancer as a function of tar level, with the lowest level (<18 mg tar) being the referent group defined as a relative risk of 1.0, and smokers of the highest tar level (>25.9 mg tar) having a relative risk of about 1.42. In the center portion of the graph, the relative risks have been adjusted by removing those individuals who were self-reported smokers at the fourth follow-up (the first follow-up for the second six year period) but were self-reported former smokers at the fifth follow-up (the last follow-up that occurred at the end of the second six year period). Since individuals who reported being former smokers during the last follow-up could have quit smoking any time during the six year period between the fourth and the last follow-up, this adjustment to the data is clearly justifiable in order to obtain a better estimate of the actual relationship of machine-derived tar yield to the relative risk for lung cancer. The change brought about by this adjustment is relatively minor, with the relative risk for the highest tar level declining from abut 1.42 to about 1.38. The right-hand side of the graph shows the relative risk as a function for tar level only for those individuals "who did not change the number of cigarettes that they reported smoking per day over the multiple follow-up measurements." According to the legend of Figure 4-5, this result has been adjusted for cigarettes per day. This group consisted of approximately one-third of all the smokers in the sample. As can be seen, there is essentially no difference in relative risk for lung cancer as a function of tar yield.

This last result, to say the least, was intriguing. As a consequence we attempted to repeat these analyses in order to determine if these results could be reproduced. In addition it was felt worthwhile to determine if similar results were obtained when these calculations were carried out for women. This analysis is discussed below. Because of the complexity of this analysis, the summary below is supplemented by a more detailed discussion of both methodology and results in Appendix A.

The analyses carried out in Chapter 4 used the baseline (questionnaire 1) values for tar level and cigarettes smoked per day. Duration, age, cigarettes per day and a first vs. second six-year follow-up indicator were used as independent variables in a SAS 'lifereg' survival analysis. Our

independent analyses were carried out using Peto analyses adjusted for grouped values of duration, age, and cigarettes per day for the first vs. second six-years follow up. Because adjustment for the first vs. second six-years follow-up separated the analysis into these two halves, it was not necessary to adjust age and duration values for the start of the second six-year period as this would have simply added six to the values for each subject for the second six-year period.

It should be noted that the tar levels shown in the monograph could not be reflected exactly in our analysis. The only source of tar level information is a single "brand and type of cigarette" variable, which groups cigarette brands according to filter/non-filter, menthol or not, nicotine level, and tar level. The original brand information is not available. The levels of this variable have overlapping tar ranges but can be grouped approximately as shown in the monograph. The results of this grouping, compared to the levels specified in Monograph 13, are listed in Table 6.

Table 6
Tar Ranges Used to Analyze CPS-I Data

Tar Level Number	Range Stated in Monograph 13	Range Included in Our Tar Level Variable
1	<18.0	7.2-17.3
2	18.0-21.5	16.7-23.0
3	21.5-25.9	21.3-25.8
4	>25.9	25.8-35.7

The details as to how these tar range groupings were obtained can be found in Appendix A. It should be noted that these minor differences in tar yield ranges between our independent analysis and the analysis carried out by Burns, et al., are undoubtedly the result of differences in methodology used to determine tar yields. The text of this section states that, "[T]he...tar levels of the cigarettes smoked were those recorded in the baseline survey for all of these analyses." However, the legend below figure 4-5 states, "[T]ar level interpolated from Reader's Digest...1959...and FTC (for years 1967-1973) data by brand and year." These two statements appear to be inconsistent. This inconsistency is somewhat resolved by the brief description of how tar and nicotine levels were obtained for CPS-I data in the Appendix to Chapter 4 (see p. 147). Information in the Appendix makes it clear that the baseline tar and nicotine data for each brand listed were obtained from the Reader's Digest survey carried out in 1959. Brand specific information for brands listed in follow-ups were obtained from FTC data. Since the years that FTC published tar and nicotine data during that period do not correspond exactly with the years of follow-up, interpolation was carried out in order to adjust the FTC tar and nicotine levels to those that might be expected to be obtained for the year of follow-up. Moreover, since a given brand specified only the "trade-mark;" e.g. Camel, a sales-weighted tar and nicotine value for all types of Camel on the market at that time was used for each brand. In that the specific data that were used to obtain tar values were not available to us, it is not surprising that we cannot exactly reproduce the tar ranges used in Monograph 13.

As noted above, there were five questionnaires in all. The first questionnaire (the baseline questionnaire in 1959) was followed, at two-year intervals, by the second, third, and fourth questionnaires. Thus within the first six-year period, we have information from four questionnaires. The fifth questionnaire was carried out six years after the fourth, so that in the second six-year period we have information only at the start and the end of the period.

The first analysis censors subjects at the questionnaire for which they first state that they are ex-smokers. The second analysis uses unchanged censoring for the first six years of follow-up, but changes the censoring for the second six years (for which there was only questionnaire 4 at the

beginning and questionnaire 5 at the end). For the second six years the subject is censored as of the fourth questionnaire if they state at the fifth questionnaire that they had quit smoking. Burns, et al., make the point that censoring individuals who indicated that they were no longer smokers in the fifth questionnaire gives a better estimate of the potential role of reduced tar, since such individuals would have had a lower risk of lung cancer. However, it should be noted that, whereas in the first analysis a subject who actually quit just after the fourth questionnaire would be censored almost six years late, in the second analysis a subject who actually quit just before the fifth questionnaire would be censored almost six years early. As a consequence, one would really not anticipate a large difference in the results from these two approaches.

In that the third analysis is far more complicated to attempt to reproduce than the first two analyses, we present here the results for the first two analyses for men, which can be directly compared to the results published in Monograph 13, and for women, where the results are not comparable. These results are displayed in Table 7, for both analyses 1 and 2.

Table 7
Relative Risk of Lung Cancer by Tar Level (Compared with Tar Level 1)

Tar Level	Figure 4-5 Odds Ratio (95% Confidence Interval)*	Peto Analysis RR (95% Confidence Interval)
Analysis I, Men		
2	1.25 (1.02, 1.55)	1.17 (0.99, 1.37)
3	1.37 (1.12, 1.65)	1.18 (0.98, 1.41)
4	1.44 (1.22, 1.75)	1.31 (1.12, 1.53)
P (Trend)	"Statistically Significant"	<0.001
Analysis 1, Women		
2	NA	1.26 (0.94, 1.69)
3	NA	1.65 (1.16, 2.34)
4	NA	2.01 (1.50, 2.69)
P (Trend)	NA	<0.001
Analysis 2, Men		
2	1.16 (0.91, 1.44)	1.16 (0.98, 1.36)
3	1.34 (1.09, 1.69)	1.17 (0.97, 1.40)
4	1.36 (1.12, 1.65)	1.28 (1.09, 1.49)
P (Trend)	Presumably Significant	0.001
Analysis 2, Women		
2	NA	1.23 (0.92, 1.65)
3	NA	1.64 (1.15, 2.34)
4	NA	1.92 (1.44, 2.58)
P (Trend)	NA	<0.001

* Confidence intervals estimated from Figure 4-5

As can be seen from inspection of Table 7, the two methodologies provide relatively comparable results. The trend in relative risk is somewhat less pronounced for the Peto analysis that we carried out; however, it is still highly significant, being <0.001 for analysis 1 and equal to 0.001 for analysis 2. Also for both tar levels 2 and 3, the difference in RR for the Peto analysis are not statistically significant from tar level 1 for both analysis 1 and 2, whereas the ORs taken from Figure 4-5 in Chapter 4 are significant for tar levels 2 and 3 for analysis 1 and for tar level 3 in analysis 2. Both the Chapter 4 results and the Peto analyses show little differences for the two analyses. The results for women show a more pronounced trend with RR as a function of tar yield than do the results for men. For both analyses 1 and 2 tar levels 3 and 4 are statistically different

from tar level 1. For women, as was the case for men, there is little difference between the results of the two analyses. As was pointed out above, this is not surprising.

Considerable difficulties were encountered in attempting to reproduce the third analysis shown in Figure 4-5. This analysis uses the same censoring as did the second analysis (see above) but includes only those individuals who smoked the same number of cigarettes per day during the 12-year follow-up period. The ORs presented in Figure 4-5 are also adjusted for cigarettes per day. Although this approach appears to be relatively straightforward in concept, there are a number of difficulties with respect to its implementation.

The first problem lies in the fact that only grouped values for cigarettes per day are available. These categories are 1-9, 10-19, 20, 21-39, 40, and 41+ cigarettes per day. To check for constant cigarettes per day across the surveys, it was only possible to determine that a subject remained within the same category. A subject initially smoking 20 cigarettes per day would be censored if he or she decreased his or her consumption by a single cigarette per day. On the other hand, a subject initially smoking 60 cigarettes per day could increase or decrease his or her consumption considerably without changing category, thereby avoiding being censored.

The second problem concerns the handling of missing data. A subject may supply a value for daily cigarette consumption for each of the five questionnaires. To avoid being censored, this subject must fall into the same consumption category each time. However, many subjects did not supply a value for each of the five questionnaires. Many people were not traced for some of the questionnaires (often, but not always, being found again at a subsequent questionnaire). Others were traced but failed to supply a value for the question about daily cigarette consumption. If all those with missing values were excluded there would be a very small number of subjects in the analysis. Other subjects quit smoking and so reduced their consumption to zero.

It was decided to be inclusive in interpreting which subjects had constant cigarettes per day. If, for the cigarettes per day values available, the subject was always in the same category, then the subject was not excluded. However, if the subject quit, this was taken as a change in consumption, and the subject was excluded. In the most extreme circumstances this meant including those who answered the cigarettes per day question in the initial questionnaire only, these subjects having not demonstrated any changes in consumption level. It is extremely important to note that even with these rules the analysis for men included only around one in five of the original subjects. This is in contrast to the text of this section in Chapter 4 that states that the group of subjects in this third analysis consisted of approximately one-third of all smokers.

Analysis 3, as well as analysis 2, suffers from the theoretical problem that they both consider deaths occurring during a period (or periods) for which exclusions are made from the at-risk population based on data recorded at the <u>end</u> of the period. For those who do not qualify for exclusion, because they continue to smoke (analysis 2) or continue to smoke at the same level of cigarettes per day (analysis 3), the analysis considers both decedents and survivors. However, for those who do qualify for exclusion (because they quit or changed the amount they smoke) the analysis excludes survivors but does <u>not</u> exclude decedents, since no data are available to demonstrate their change in habit. This exclusion from the denominator, but not the numerator of risk calculations, may cause substantial bias to estimated relative risks, especially when the tar groups being compared differ in their propensity to quit or change the amount they smoke.

To illustrate this bias, consider a simple study with one time period and two groups of equal size. In the high tar group all the subjects are assumed to continue smoking the same amount, but in the low tar group half of them increase the amount they smoke. If tar level and increasing amount smoked had no effect on risk, it can be seen that one would observe a low/high tar relative risk of about 2. This is because the low tar group would have about the same number of deaths as occurred in the high tar group, since we hypothetically assume no decrease in risk, but half the

number at risk, since half of the low tar risk was censored because of change in cigarettes smoked per day.

To avoid this bias and yet obtain a meaningful third analysis, we tried an additional approach in which we used only questionnaires 1 (baseline questionnaire) and 4 (first questionnaire of the second six-year follow-up) to identify those who quit smoking or changed consumption category (thus considering only those who did not demonstrate a change in the amount they smoked per day). Then, with these subjects excluded, we studied deaths in the second six-year follow-up period only.

The results of the third analysis, carried out using three different sets of assumptions are shown in Figure 8 for both men and women. The results of the first column determine relative risks using data for all questionnaires and provide fully adjusted relative risks. The results in the second column determine relative risks using data for all questionnaires and provide relative risks adjusted for all factors except for cigarettes per day. The last column determines relative risks fully adjusted; however, as outlined above relative risks are determined for the second six-year follow up (questionnaires 4 and 5) compared to the first six-year follow up and defining the population from questions 1 and 4. This was done to eliminate the bias discussed above.

Table 8
Relative Risk of Lung Cancer by Tar Level (Compared with Tar Level 1)

Tar Level	Fig. 4-5 OR (95% Confidence Interval)*	Peto Analysis RR (95% Confidence Interval)		
		All Adjustments	Adjustments Minus Cigs/Day	Q's 4-5 Only: Population Defined Using Q's 1-4
Analysis 3, Men				
2	0.96 (0.68, 1.38)	1.24 (0.95, 1.63)	1.27 (0.98, 1.65)	1.56 (0.98, 2.47)
3	0.93 (0.68, 1.33)	1.06 (0.78, 1.45)	1.01 (0.75, 1.36)	1.02 (0.60, 1.72)
4	0.97 (0.70, 1.35)	1.09 (0.84, 1.42)	1.10 (0.85, 1.42)	1.17 (0.74, 1.84)
P (Trend)	Not Significant	0.68	0.66	0.44
Analysis 3, Women				
2	NA	1.17 (0.71, 1.92)	1.21 (0.75, 1.96)	1.12 (0.58, 2.17)
3	NA	1.92 (1.12, 3.30)	2.01 (1.19, 3.37)	1.91 (0.90, 4.08)
4	NA	2.02 (1.24, 3.28)	2.06 (1.30, 3.27)	2.31 (1.19, 4.47)
P (Trend)	NA	0.001	<0.001	0.01

* Confidence intervals estimated from Figure 4-5

There are several conclusions that can be drawn from Table 8. The first is that there is not a major difference in the calculated relative risks for most of the tar levels as a consequence of the different set of assumptions made. The second is that the pattern for men and women are quite different. For those women who can be considered to have smoked a constant number of cigarettes per day throughout the entire period of follow-up, there remains a very significant trend for increasing relative risk as a function of tar level. This is not the case for men. There is a non-statistically significant increase for tar level 2 compared to tar level 1. However, for tar levels 3 and 4 the increase is less than that observed for tar level 2. Although this pattern does not exactly match the results obtained in Chapter 4 using survival analysis, both results are comparable in that no statistically significant trend was observed. Lastly, it should be noted that the confidence intervals are quite wide for both men and women, since the sample size for this analysis was only about 20% of the total sample for the Peto analysis and was stated to be only about 33% of the total sample for the analysis summarized in Figure 4-5 in Chapter 4.

An intriguing question, which was not raised in Chapter 4, is whether or not there is a particular level of cigarettes per day that is more frequently represented in the sample of individuals claiming to have smoked the same numbers of cigarettes than in the total sample itself. The possibility exists, for example, that individuals who consistently reported smoking the same number of cigarettes per day were primarily smokers who smoked very few cigarettes per day ("chippers") and, therefore, would have had a very low relative risk for lung cancer irrespective of tar level. The total number of white males who consistently reported smoking the same number of cigarettes per day, more accurately the same range of numbers of cigarettes per day, on each of the five questionnaires was 32,853. The percentages of white male smokers reporting the same number on each questionnaire for each category of cigarettes smoked were: 1-9 cigarettes per day, 7.5%; 10-19 cigarettes per day, 14.5%: 20 cigarettes per day, 51.4%; 21-39 cigarettes per day, 14.5%; 40 cigarettes per day, 9.7%; and 41+ cigarettes per day, 2.3%. The results from the total sample (baseline) were: 1-9 cigarettes per day, 8.0%; 10-19 cigarettes per day, 17.9%: 20 cigarettes per day, 38.5%; 21-39 cigarettes per day, 22.1%; 40 cigarettes per day, 10.4%; and 41+ cigarettes per day, 2.5%. As can be seen from the above results, slightly more than half of the men who reported smoking the same number of cigarettes on each of the five questionnaires indicated that they smoked exactly 20 cigarettes per day. This is most likely a consequence of the fact that the average smoker, when asked to report his daily cigarette consumption, responds 'one pack a day.' This point is perhaps confirmed by the fact that the percentage of individuals within the total sample stating that they smoked 20 cigarettes per day was noticeably less (38.5% compared to 51.4%), while the portion of the total sample reporting to have smoked 10-19 and 21-39 cigarettes was greater than in the group that reported smoking the same number of cigarettes during each follow-up. The results for white women are as follows. The total number who consistently reported the same number of cigarettes per day was 33,402. The percentages of white female smokers reporting the same number on each questionnaire for each category of cigarettes smoked were: 1-9 cigarettes per day, 20.1%; 10-19 cigarettes per day, 27.0%; 20 cigarettes per day, 44.3%; 21-39 cigarettes per day, 5.6%; 40 cigarettes per day, 2.7%; and 41+ cigarettes per day, 0.2%. The results of the total sample (baseline) were: 1-9 cigarettes per day, 24.4%; 10-19 cigarettes per day, 30.8%; 20 cigarettes per day, 31.1%; 21-39 cigarettes per day, 8.9%; 40 cigarettes per day, 3.0%; and 41+ cigarettes per day, 0.3%. Once again, the largest category of women reporting smoking the same number of cigarettes per day on each questionnaire were those who smoked 20 cigarettes a day. However, in this case the percentage was slightly less than 50%. Nevertheless, as was the case for men, the percentage who reported smoking exactly 20 cigarettes per day for each follow up was considerably greater than the percentage of women who reported smoking 20 cigarettes per day at baseline. There are two other differences between women and men that can be noted. One is that the number of women reporting smoking the same number of cigarettes per day on each questionnaire is greater than the number of men. This is despite the fact that there were more male smokers than female smokers in CPS-I. Whether this fact suggests that women are less likely to change the number of cigarettes smoked per day or suggests that women are more accurate in their reporting cannot be determined. Secondly, and not at all surprisingly, women tend to smoke fewer numbers of cigarettes per day than do men. In summary, based on the above analysis, it is not certain if individuals who report a constant number of cigarettes per day at each follow-up truly represent a group with "more stable smoking practices with regard to number of cigarettes smoked per day," or a group that was more likely to simply respond with 'a pack a day' at each follow up.

Trend tests were carried out for male smokers for each category of cigarettes smoked to determine if any significant trend as a function of tar level could be observed for a given number of cigarettes smoked per day. No statistically significant trend was observed. For women, a statistically significant trend for the RR of lung cancer as a function of tar level was observed for smokers of 10-19 cigarettes per day and 20 cigarettes per day. These two categories of cigarettes smoked per day were the two largest, accounting for 72.3% of all women smokers in this analysis. Given that the total sample of white female smokers showed a significant trend for RR of lung cancer as a function of tar level, it is not surprising that smokers of these two categories of

cigarettes per day also showed a statistically significant trend. The data for these calculations are given in Appendix A.

Following this lengthy discussion of a single section in Chapter 4, it would not be surprising if the reader of this review was no longer aware of exactly what the purpose of this section was. The concluding paragraph of Chapter 4 clearly indicates this purpose:

> "When using the baseline values for tar and cigarettes smoked per day, it was impossible to eliminate the influence of compensatory changes in cigarettes per day that occurred prior to the baseline measurement. However, by selecting a group that did not change the number of cigarettes that they reported smoking during the survey, it is possible that a group may have been identified that also had more stable smoking practices with regard to the number of cigarettes smoked per day prior to entry into the study. When this group was examined using the baseline number of cigarettes smoked per day and tar levels, there was no effect of tar level of the cigarette smoked on the odds ratio for lung cancer risk. This suggested that, at least in this group with stable smoking behavior, there was no relationship between the type of cigarette smoked and the degree of lung cancer risk. However, it was not possible to conclude from these analyses that the difference in lung cancer risk by type of cigarette smoked in the larger group containing all smokers was due to compensatory changes in the number of cigarettes smoked per day."

The key points from this concluding paragraph are: 1) for the group with "stable smoking behavior" there was no relationship between type of cigarette smoked and lung cancer risk, and 2) it was not possible to conclude from this analysis if "the difference in lung cancer risk by type of cigarette smoked in the larger group containing all smokers was due to compensatory changes in the number of cigarette smoked per day." As a consequence, although Chapter 4 presents some evidence from a sub-set CPS-I suggesting the lack of correlation between lung cancer risk and tar level of cigarette smoked, the authors themselves concede that this evidence cannot be used to draw conclusions regarding the total sample.

Our independent analysis discussed above basically qualitatively confirms the results of Chapter 4 for male smokers. However, for female smokers the same analysis demonstrates a highly significant trend for lung cancer risk and tar level of cigarettes smoked, even when results are adjusted for cigarettes per day. As a consequence, it is difficult to determine if one can draw any meaningful conclusions from this analysis at all. It would seem most circumspect to simply describe this analysis as an interesting result that cannot be explained, given the lack of any type of confirmatory data.

H. Cardiovascular Disease

Chapter 4 next turns its attention to studies that have compared either filter smokers vs. non-filter smokers or smokers of low-tar cigarettes vs. smokers of high-tar cigarettes with respect to risk of cardiovascular disease. These data are summarized in Table 4-2. Table 9 below tabulates the studies included in Table 4-2 as well as some studies that were not covered by Burns, et al. Because of the smaller number of studies for cardiovascular disease as compared to lung cancer, Table 9 includes studies that have compared both filter vs. non-filter and low-tar vs. high-tar. Of the 42 relative risks in the table, 29 are below 1.00 (12 statistically significant), 1 is equal to 1.00, and 12 are above 1.00 (none significantly). It should be noted that the largest studies, the ACS first million person study of Hammond, et al. (1976), the huge case-control study of Parish, et al. (1995), and the combined analysis of four cohorts by Tang, et al. (1995), all show significant decreases.

In attempting to carry out meta-analysis, it seemed sensible to avoid dependence between estimates by (i) considering estimates unadjusted and adjusted for cigarettes per day separately,

Table 9
Epidemiological Studies of Filter (Low-Tar) Cigarettes vs. Non-Filter (High-Tar) Cigarettes for Cardiovascular Disease (CVD)

Citation	Population	Time Period	RR or OR Unadjusted for Cigts./Day	RR or OR Adjusted for Cigts./Day	Remarks
Hammond, E. C., et al., *Environ. Res.*, 12: 263-274, 1976[a]	12-year follow-up of CPS-I, a prospective mortality study of over 1 million men and women	1960-1972		1960-1966 0.93 (M) 95% CI, 0.84-1.04 0.82 (F) 95% CI, 0.70-0.96 1966-1972 0.81 (M) 95% CI, 0.69-0.95 0.81 (F) 95% CI, 0.68-0.97	RRs compare low-tar (<17.6 mg/cigarette) smokers to high-tar (25.8-35.7 mg/ cigarette) smokers. In addition to adjustment for cigarettes per day, RRs are adjusted for age, race, age at start, urban/rural, occupation, education, history of lung cancer, CHD, and stroke, diastolic bp, exercise, obesity index, coffee and tea, alcohol, and social class. Confidence limits were calculated from data provided in the citation.
Castelli, W. P., et al., *Lancet*, ii: 109-113, 1981[b]	Data from the 7th biennial examination (14 year follow-up) of the Framingham study involving 1605 men	1963-1967	0.92 (M) 95% CI, 0.55-1.50		RR compares smokers of filter cigarettes to smokers of non-filter cigarettes. Although the RR is not adjusted for cigarettes per day, it is adjusted for age, blood pressure, and cholesterol level.
Sorlie, P. D., et al., *Preventive Med.*, 11: 304-316, 1982[b]	Prospective study in over 9000 men, aged 45-64 years, in Puerto Rico investigating the association of coronary heart disease incidence associated with smoking	1965-1973	1.02 (M) 95% CI, 0.68-1.53		RR compares smokers of filter cigarettes to smokers of non-filter cigarettes. RR and confidence limits were calculated from data provided in the citation. RR is adjusted for age and depth of inhalation.

Citation	Population	Time Period	RR or OR Unadjusted for Cigts./Day	RR or OR Adjusted for Cigts./Day	Remarks
Higenbottam, T., et al., *J. Epidemiol. Community Health*, 36: 113-117, 1982	10-year follow-up of 17, 475 male civil servants, aged 40-54, and a sample of male British residents	1965-1975	0.84 (M) 95% CI, 0.65-1.08		RR compares low-tar (19-23 mg tar/cigarette) to high-tar (≤33 mg tar/cigarette). RR is adjusted for age, inhalation, and employment grade. RR and confidence limits are calculated from data provided in the citation.
Todd, G. F. et al., *Journal Epidemiol. Community Health*, 32: 267-274, 1978.	12.4-year prospective follow-up of 10,063 subjects aged 35-69 from a random sample of the population in Great Britain	1965-1977			This paper provides considerably less data than an analysis carried out on the same study by Reid cited in the Lee and Garfinkel review (1981). These data are listed in the next entry.
Reid, D. D., taken from data reported in Lee, P. N., and Garfinkel, L., *J. Epidemiol. Community Health*, 35: 16-22, 1981	12.4-year prospective follow-up of 10,063 subjects aged 35-69 from a random sample of the population in Great Britain	1965-1977		0.84 (M) 95% CI, 0.65-1.08 0.91 (F) 95% CI, 0.57-1.46	RRs compare smokers of filter cigarettes to smokers of non-filter cigarettes. RRs adjusted for cigarettes per day are also adjusted for age, age at start and depth of inhalation. RR for males is based on 253 deaths, while RR for females is based on 76 deaths
Hawthorne, V. M., and Fry, J. S., *J. Epidemiol. Community Health*, 32: 260-266, 1978	Prospective follow-up of 18,786 people attending a multiphasic screening examination	1965-1977		1.05 (M) 95% CI, 0.78-1.41	RR compares smokers of filter cigarettes to smokers of non-filter cigarettes. RR adjusted for cigarettes per day is also adjusted for age and study center. RR is based on 200 deaths. Confidence limits were calculated from data presented in the citation.

Citation	Population	Time Period	RR or OR Unadjusted for Cigts./Day	RR or OR Adjusted for Cigts./Day	Remarks
Borland, C., et al., *BMJ*, 287: 1583-1586, 1983	Prospective 10-year follow-up of the Whitehall study involving 4,910 male smokers of cigarettes with known CO yields (same population is Higgenbottom above)	1967-1979			Although this study cites a RR of 0.67 for smokers of "low" CO cigarettes compared to smokers of "high" CO cigarettes, this RR cannot be used in a meta-analysis comparing high-tar to low-tar. This is because, as the authors point out, the observed correlation between CO and tar delivery in their sample was a statistically non-significant R = 0.5.
Tang, J.-L., et al., *BMJ*, 311: 1530-1533, 1995	Four prospective mortality studies from the United Kingdom	1967-1982		0.93 (M) 95% CI, 0.80-1.07 0.77 (M) 95% CI, 0.61-0.97	The first RR compares smokers of filter cigarettes to those of non-filter cigarettes. The second RR is based on a 15 mg reduction in tar. Both RRs are adjusted for cigarettes per day and are also adjusted for age and study center.
Dean, G., et al., *Report on a Second Retrospective Mortality Study in North-East England – Part 1. Factors Related to Mortality from Lung Cancer, Bronchitis, Heart Disease and Stroke in Cleveland County, with Particular Emphasis on the Relative Risks Associated with Smoking Filter and Plain Cigarettes.*[b]	Case-control study of 571 deceased male coronary heart disease cases and 2,563 male population controls from Cleveland County, UK	1971-1972	0.39 (M) 95% CI, 0.23-0.64	0.49 (M) 95% CI, 0.31-0.77	ORs compare smokers of filter cigarettes to smokers of non-filter cigarettes. OR unadjusted for cigarettes per day and confidence limits for both ORs were calculated from data provided in the citation. OR adjusted for cigarettes per day was also adjusted for age.

Citation	Population	Time Period	RR or OR Unadjusted for Cigts./Day	RR or OR Adjusted for Cigts./Day	Remarks
Kuller, L. H., et al., *Preventive Med.*, 20: 638-654, 1991	10.5-year follow-up of 12,866 randomized MRFIT participants (taken from a total sample of 361,662 men at initial screening) all of whom were self-reported smokers	1972-1985	0.93 (M) 95% CI, 0.64-1.35 0.83 (M) 95% CI, 0.59-1.18	0.84 (M) 95% CI, 0.61-1.16 0.79 (M) 95% CI, 0.56-1.09	The first RRs represent a comparison of smokers of cigarettes with ≤15 mg tar compared to those with ≥20 mg tar. The second RRs represent a comparison of smokers of cigarettes with ≤1.0 mg nicotine compared to those with ≥1.5 mg nicotine. RRs and confidence limits were calculated from data presented in the citation. Unadjusted RRs were not adjusted for any factor. RRs adjusted for cigarettes per day were also adjusted for age, cholesterol level, and blood pressure.
Ockene, J. K., et al., *Am. J. Public Health*, 80: 954-958, 1990[b]	Prospective study of 12,866 men enrolled in the Multiple Risk Factor Intervention Trial (MRFIT) in the US	1973-1985		0.72 (M) 95% CI, 0.44-1.16	RR compares smokers of filter cigarettes to smokers of non-filter cigarettes. RR is calculated from regression coefficient. RR is adjusted for age, cigarettes per day, age at start, tar, nicotine, alcohol, blood pressure, cholesterol, and serum thiocyanate.
Benhamou, E., et al., *Br. J. Cancer*, 55: 91-95, 1987	Case-control study of 1,625 lung cancer patients and 3,091 hospital controls. This report includes females only – 96 cases and 192 controls	1976-1980			Although this citation is listed in Table 4.2 of Chapter 4, the data are for lung cancer and not for cardiovascular disease.

Citation	Population	Time Period	RR or OR Unadjusted for Cigts./Day	RR or OR Adjusted for Cigts./Day	Remarks
Nyboe, J., et al., *Am. Heart J.*, 122: 438-447, 1991[b]	6.5-year follow-up of 20,000 men and women in Denmark (Copenhagen City Heart Study) selected at random from the population of Copenhagen	1976-1983		0.67 (M+F) not significant	RR adjusted for age, sex, education, cholesterol, diabetes, blood pressure, family history of MI or stroke, obesity index, and depth of inhalation. Confidence limits could not be estimated from data provided. RR based on 251 cases.
Alderson, M. R., et al., *J. Epidemiol. Community Health*, 39: 286-293, 1985	Case-control study of 12,693 in-patients	1977-1982	1.50 (M) 95% CI, 0.65-3.45 2.87 (M) 95% CI, 0.98-8.41 0.21 (F) 95% CI, 0.07-0.63 1.19 (F) 95% CI, 0.57-2.46	1.78 (M) 95% CI, 0.77-4.10 2.67 (M) 95% CI, 0.91-7.83 0.24 (F) 95% CI, 0.08-0.73 1.32 (F) 95% CI, 0.64-2.73	ORs compare smokers of only filter cigarettes to smokers of only non-filter cigarettes. The first OR listed for both males and females represents the age group 35-54. The second OR represents the age group 55-74. Unadjusted ORs and all confidence limits were calculated from data provided in the citation. ORs adjusted for cigarettes per day are also adjusted for age.
Petitti, D. B., and Friedman, G. D., *J. Chron. Dis.*, 38: 581-588, 1985[c]	4-year prospective follow-up of 16,270 current regular smokers and 42,113 subjects who never used any form of tobacco	1979-1982		0.80 (M+F) 95% CI, 0.63-1.01 0.85 (M+F) 95% CI, 0.68-1.06	RRs are based on a decrease in tar of 5 mg. The first RR is calculated for the association of a 5 mg tar reduction with acute myocardial infarction, while the second RR is calculated for the association of a 5 mg decrease for other ischemic heart disease. The RRs are also adjusted for age, sex, race, obesity index, cholesterol level, blood pressure, and alcohol consumption. Confidence limits calculated from data provided in citation.

Citation	Population	Time Period	RR or OR Unadjusted for Cigts./Day	RR or OR Adjusted for Cigts./Day	Remarks
Kaufman, D. W., et al., *N. Engl. J. Med.*, 308: 409-413, 1983[b]	Case-control study in the northeastern US to evaluate the risk of the first nonfatal myocardial infarction in men all between the ages of 30 and 54; the study involved 502 cases and 835 hospital controls	1980-1981	1.19 (M) 95% CI, 0.74-1.91		OR is adjusted for age, area of residence, blood pressure, cholesterol level, diabetes, family history of myocardial infarction or stroke, personality, alcohol consumption, religion, and marital status. OR and confidence limits were calculated from data provided in the citation.
Bosetti, C., et al., *Preventive Med.*, 29: 343-348, 1999[b]	Two case-control studies in Italy including 429 women and 801 men with acute myocardial infarction and 863 female and 976 male controls in hospital for acute conditions, excluding cardiac, cerebrovascular, and neoplastic disease, unrelated to smoking	1983-1992	1.15 (M) 95% CI, 0.77-1.72 0.71 (F) 95% CI, 0.39-1.30		ORs compare reduction in risk for smokers of cigarettes with >10 mg tar to smokers of cigarettes with <15 mg tar. ORs are adjusted for age, education, cholesterol level, diabetes, blood pressure, family history of myocardial infarction or stroke, coffee consumption, alcohol consumption and obesity index. OR for males, based on 441 cases, and OR for females based on 174 cases. ORs and confidence limits calculated from data provided in the citation.

Citation	Population	Time Period	RR or OR Unadjusted for Cigts./Day	RR or OR Adjusted for Cigts./Day	Remarks
Palmer, J. R., et al., *N. Engl. J. Med.*, 320: 1569-1573, 1989	Case-control study of 910 women with a first myocardial infarction under age 65 and 2,375 hospital controls in 71 participating hospitals in Massachusetts, Rhode Island, Connecticut, and New York	1985-1988	1.12 (F) 95% CI, 0.60-2.11		OR based on smokers of cigarettes delivering ≤40 mg nicotine compared to smokers of cigarettes delivering ≥1.30 mg nicotine. OR was adjusted for age, blood pressure, history of heart disease, diabetes, cholesterol level, menopausal status, obesity index, personality, exercise, education, area of residence, occupation, estrogen, and coffee and alcohol consumption. OR based on 70 cases.
Negri, E., et al., *Brit. Med. J.*, 306: 1567-70, 1993	Case-control study of 916 patients with acute myocardial infarction without history of ischemic heart disease and 1,106 hospital controls in a multi-center Italian study	1988-1989	1.03 (M+F) 95% CI, 0.56-1.87	1.00 (M+F) 95% CI, 0.56-2.00	ORs compare smokers of <10 mg tar cigarettes to smokers of >20 mg cigarettes. Both ORs are adjusted for age, sex, education, cholesterol level, diabetes, blood pressure, family history of myocardial infarction or stroke, obesity index, and coffee consumption. Confidence limits calculated from data provided in the citation.

Citation	Population	Time Period	RR or OR Unadjusted for Cigts./Day	RR or OR Adjusted for Cigts./Day	Remarks
Parish, S., et al., *Brit. Med. J.*, 311: 471-477, 1995[d]	Case-control study in the United Kingdom in the early 1990s with 13,926 survivors of myocardial infarction recently discharged from hospitals and 32,389 relatives (controls)	Early 1990s	0.83 (M+F) 95% CI, 0.73-0.94 0.96 (M+F) 95% CI, 0.81-1.12	0.86 (M+F) 95% CI, 0.75-0.98 0.99 (M+F) 95% CI, 0.84-1.17	ORs compare smokers of low-tar cigarettes (<10 mg, 7.5 mg mean) to smokers of medium tar cigarettes (≥10 mg, 13.3 mg mean). The first ORs refer to individuals 30-59 years of age, and the second ORs refer to individuals 60-79 years of age. All ORs were adjusted for age and sex. ORs and confidence limits were calculated from data provided in the citation.
Sauer, W. H., *Arch. Intern. Med.*, 162: 300-306, 2002[b]	Case-control study in eastern Pennsylvania of first myocardial infarction in smokers aged 30 through 65 years of age consisting of 587 cases and 2685 community controls	1995-1997	0.53 (M+F) 95% CI, 0.38-0.75	0.45 (M+F) 95% CI, 0.30-0.68	ORs compare smokers of cigarettes with tar deliveries of ≤6 mg to smokers of cigarettes with tar deliveries of >12 mg. OR unadjusted for cigarettes per day is not adjusted for any factor. OR adjusted for cigarettes per day is adjusted for age, sex, race, education, exercise, smoking duration, obesity index, history of heart disease, diabetes, blood pressure, cholesterol level, vitamin use, and family history of myocardial infarction.

a. Reference provided in Chapter 4 is to the review by Lee, as opposed to the original article by Hammond, et al.
b. Not covered in Chapter 4
c. Relative risks given in Chapter 4 are for a 5 mg increase in tar. The relevant relative risks; that is, for a 5 mg decrease in tar are the reciprocals of those given in Chapter 4 and are correctly cited in Table 9 above.
d. Odds Ratio cited by Burns, et al., compares smokers of medium-tar cigarettes to smokers of low-tar cigarettes; e.g. the excess risk attributable to the higher tar cigarettes. The OR that expresses the reduction in risk for individuals smoking the lower tar cigarettes is correctly expressed in Table 9 above.

(ii) omitting estimates on a per mg tar reduction, which are not really comparable, and (iii) by only choosing estimates for one exposure index for a given study/sex/period (so choosing tar rather than nicotine estimates for the Kuller, et al. (1991) study). One must also exclude estimates without confidence limits. This gives 19 adjusted estimates and 17 unadjusted estimates for meta-analysis.

The data adjusted for cigarettes per day gave an overall fixed-estimates relative risk estimate of 0.87 (95% CI, 0.83-0.92) and a random-effects estimate of 0.86 (95% CI, 0.78-0.93). The data unadjusted for cigarettes per day gave a similar overall fixed-effects relative risk estimate of 0.87 (95% CI, 0.80-0.94) and a random-effects estimate of 0.88 (95% CI, 0.75-1.02). Three conclusions can be drawn from these meta-analyses. The first is that, as is the case for lung cancer, tar reduction, determined either by a comparison of filter to non-filter cigarettes or low-tar to higher tar cigarettes, demonstrates a reduction in cardiovascular risk. Three of the four meta-analyses show a statistically significant decrease in risk. The second is that the reduction in risk is less than was observed for lung cancer. The last conclusion is that adjusting for cigarettes per day made absolutely no difference as to the degree of cardiovascular disease reduction.

The meta-analytic relative risk for the risk estimates adjusted for cigarettes per day had significant heterogeneity ($\chi^2 = 38.61$ on 18 df, $p = 0.003$). The largest contributor to the heterogeneity was the low estimate of 0.45 in the Sauer, et al. (2002) study. Removing this study substantially reduced the heterogeneity ($\chi^2 = 28.36$ on 17 df, $p = 0.04$) but did not change the estimates much (fixed effects, 0.88, 95% CI, 0.84-0.93 and random effects, 0.88, 95% CI, 0.81-0.95). The data unadjusted for cigarettes per day also had significant heterogeneity ($\chi^2 = 38.79$ on 16 df, $p = 0.001$). Here the major contributors to the heterogeneity were the low estimates of 0.39 in the Dean, et al. (1977) study and of 0.53 in the Sauer , et al. (2002) study. Removing these studies eliminated the significant heterogeneity ($\chi^2 = 20.05$ on 14 df, $p = 0.13$) and slightly increased the estimates (fixed effects, 0.91, 95% CI, 0.84-0.98 and random effects, 0.94, 95% CI, 0.84-1.06). Three of the four pooled relative risks still remain, however, statistically significant. It should be noted that restricting attention to the unadjusted data means that the large Hammond (1976) study is no longer included.

There is one difficulty in establishing the most meaningful estimate of the reduction in cardiovascular risk as a function of reduction in tar yield that must be pointed out. This is the fact that the relative risk for the association of cardiovascular disease with smoking reaches a maximum at around age 45 and then declines. By age 65, the relative risk for smokers compared to non-smokers has declined substantially, although absolute risk continues to increase with age. There are a large number of epidemiological studies that have demonstrated this effect. A good example is the US Veteran's study (Kahn, H. A., 1966). The potential role this factor may have in attenuating the apparent extent of risk reduction can be seen from three studies in Table 6. The first is the Alderson, et al. (1985) study. This study determined ORs for two age groups, 35-54 and 55-74. The relative risk for filter smokers compared to non-filter smokers is clearly lower for both males and females, when comparing the younger group to the older group. The data for females in the younger age category show a very significant decrease in cardiovascular disease risk; however, for males both age categories exhibit an increase in risk. The second study is the Parish, et al. (1995) study where once again ORs were calculated for two age groups, in this case 30-59 and 60-79. A statistically significant decrease in risk was noted for the younger age group, whereas no decrease in risk was observed for the older age group. Lastly, attention should be called to the Sauer, et al. (2002) study. This study showed a 50% decrease in cardiovascular disease risk, perhaps because it analyzed a population restricted to 30-65 years of age and focused on very low-tar cigarettes (<6 mg tar).

The first sentence of Burns', et al., concluding paragraph to this section is as follows:

"In summary, while the data are not as compelling for alterations in CHD risk compared to lung cancer risk among populations who smoke low-yield cigarettes, several well-conducted epidemiological studies have demonstrated a difference in cardiovascular risk among those who smoke low-yield cigarettes when the analyses were controlled for number of cigarettes smoked per day."

As was pointed out above, the data do demonstrate "a difference in cardiovascular risk among those who smoke low-yield cigarettes", and "the data are not as compelling for alterations in CHD risk compared to lung cancer." However, as was also shown, the results are the same irrespective of whether the results were controlled or not controlled for cigarettes smoked per day. As a consequence, it has been demonstrated that "this difference in CHD experience" cannot be attributed to "differences introduced by controlling for intensity and duration of smoking in these studies."

I. Chronic Respiratory Symptoms and Disease

This section deals with studies that have compared either filter smokers vs. non-filter smokers or smokers of low-tar cigarettes vs. smokers of high-tar cigarettes with respect to risk of chronic respiratory symptoms and disease; namely, emphysema and chronic bronchitis. These data are summarized in Table 4-3. Table 10 below tabulates the studies included in Table 4-3. Unlike the situation for lung cancer and cardiovascular disease, most of the studies included in Table 10 are also included in Table 4-3. The one exception is the Dean study listed in Table 10. Although Table 4-3 also includes a Dean, et al., reference (1978), it covers respiratory symptoms only, rather than a point estimate for an association with a given disease states. Also, it should be noted that Table 10 includes a number of studies for which no RR (or OR) is listed. As a consequence, such results can not be included in a meta-analysis.

All of the studies in Table 10 provided estimates that were adjusted at least for age and cigarettes per day (or in one study, pack years). Of these 11 RRs (or ORs), 8 are below 1.00 (3 statistically significantly), 1 is equal to 1.00 and 2 are above 1.00 (neither statistically significantly). Omitting estimates on a per mg tar reduction basis, which are not strictly comparable, the fixed-effects meta-analysis relative risk estimate is 0.74 (N = 9, 95% CI, 0.62-0.88), with some heterogeneity (χ^2 = 21.0 on 9 df, p = 0.013), and the random-effects estimate is 0.70 (N = 9, 95% CI, 0.53-0.93).

Three studies provided sex-specific estimates unadjusted for cigarettes per day. Compared with the adjusted results, the unadjusted RR (or OR) estimates are slightly lower in three cases (Lange/females, Alderson/females, and Dean/males) but quite similar otherwise.

As was the case for lung cancer and cardiovascular disease, these data would appear to suggest an approximately 25-30% statistically significant decrease in risk of chronic respiratory disease associated with smoking of reduced tar cigarettes. This result, therefore, seems to be at considerable odds with the conclusions of this section of Chapter 4, which states that, "[I]n summary, there is little evidence for a substantial difference in mortality from chronic obstructive lung disease among smokers who use low-yield cigarettes." Given that the data are as limited as they are, either conclusion is actually supportable, particularly when one looks at the data only qualitatively and when, as Burns, et al., have done, the data are looked at by "category." For instance, Burns, et al., point out that The CPS-I 12-year follow-up (Hammond, et al.,1976) demonstrated a reduced death rate from emphysema, whereas other studies (Tang, et al., 1995; Lang, et al., 1992; and Pettiti and Friedman, 1985) did not demonstrate a similar reduction. However, Burns, et al., chose to select the RR of 0.94 for the Tang study, based on a filter vs. non-filter comparison, whereas Table 7 lists a RR of 0.78, based on a comparison of a decrease in 15 mg cigarette tar yield. This RR, for men, is exactly equal to the RR for men reported by Hammond, et al. The choice to include this RR in Table 7, however, has no bearing on the meta-analysis, since it was not included. As pointed out above, it was based on a per mg tar reduction basis, and therefore was omitted. From a qualitative sense, however, it is probably more logical to

Table 10
Epidemiological Studies of Filter (Low-Tar) Cigarettes vs. Non-Filter (High-Tar) Cigarettes for Respiratory Disease

Citation	Population	Time Period	RR or OR Unadjusted for Cigts./Day	RR or OR Adjusted for Cigts./Day	Remarks
Hammond, et al., *Environ. Res.*, 12: 263-274, 1976[a]	12-year follow-up of CPS-I, a prospective mortality study of over 1 million men and women	1960-1972		0.78 (M) 95% CI, 0.53-1.14 0.59 (F) 95% CI, 0.32-1.07	RRs for emphysema compare smokers of low-tar cigarettes (<17.6 mg/cigarette) to smokers of high-tar cigarettes (25.8-35.7 mg/cigarette). In addition to adjustment for cigarettes per day, RRs are adjusted for age, race, age at start, urban/rural, occupation, education, history of lung cancer, and history of CHD. Confidence limits were calculated from data provided in the citation.
Hawthorne, V. M., and Fry, J. S., *J. Epidemiol. Community Health*, 332; 260-266, 1978	Prospective follow-up of 18,786 people attending a multiphasic screening examination	1965-1977		0.72 (M) 95% CI, 0.29-1.79	RR for chronic bronchitis compares filter cigarette smokers to non-filter cigarette smokers. RR is adjusted for age and study center as well as for cigarettes per day. Confidence limits were calculated from data provided in the citation.
Tang, J. L., et al., *Brit. Med J.*, 311: 1530-1533, 1995[b]	Four prospective mortality studies from the United Kingdom	1967-1982		0.94 (M) 95% CI, 0.64-1.37 0.78 (M) 95% CI, 0.41-1.48	RRs are for COLD. The first RR compares filter smokers to non-filter smokers, while the second is the RR per 15 mg tar reduction. RRs adjusted for cigarettes per day are also adjusted for age and study center.

Citation	Population	Time Period	RR or OR Unadjusted for Cigts./Day	RR or OR Adjusted for Cigts./Day	Remarks
Sparrow, D., et al., *Am. Rev. Resp. Dis.*, 127: 56-58, 1983	383 current smokers enrolled in a longitudinal study of aging who had spirometry performed 5 years apart	1969-1980			In a multiple regression analysis, tar level did not influence FVC or FEV_1 at baseline or change in these measures at follow-up.
Dean, G., et al., *Report on a Second Retrospective Mortality Study in North-East England – Part 1. Factors Related to Mortality from Lung Cancer, Bronchitis, Heart Disease and Stroke in Cleveland County, with Particular Emphasis on the Relative Risks Associated with Smoking Filter and Plain Cigarettes.*	Case-control study of 530 deceased male and 218 deceased female chronic bronchitis cases and 2,563 male and 2,958 female population controls from Cleveland County, UK	1969-1972	0.39 (M) 95% CI, 0.23-0.66 0.25 (F) 95% CI, 0.12-0.53	0.58 (M) 95% CI, 0.35-0.95 0.27 (F) 95% CI, 0.13-0.57	ORs for chronic bronchitis compare smokers of filter cigarettes to smokers of non-filter cigarettes. ORs not adjusted for cigarettes per day are not adjusted for any factor. ORs adjusted for cigarettes per day are also adjusted for age. As noted in the text, Table 4-3 in Monograph 13 includes a Dean, et al. reference that deals with respiratory symptoms only.
Lange, P., et al., *Eur. Resp. J.*, 5: 1111-1117, 1992	6,511 men and 7,703 women selected randomly after age stratification from the general population in Copenhagen, followed for 13 years	1976-1989	1.23 (M) 95% CI, 0.70-2.19 1.07 (F) 95% CI, 0.59-1.94	1.20 (M) 95% CI, 0.70-2.00 1.30 (F) 95% CI, 0.60-2.60	ORs for COPD-related disease compare filter smokers to non-filter smokers. ORs unadjusted for cigarettes per day are adjusted for age. ORs shown in the "adjusted for cigarettes per day" column, are actually adjusted for pack years of smoking as well as for age.

Citation	Population	Time Period	RR or OR Unadjusted for Cigts./Day	RR or OR Adjusted for Cigts./Day	Remarks
Alderson, M. R., et al., *J. Epidemiol. Community Health*, 39: 286-293, 1985	Case-control study of 12,693 in-patients	1977-1982	0.26 (M) 95% CI, 0.10-0.64 0.67 (F) 95% CI, 0.36-1.28	0.25 (M) 95% CI, 0.10-0.64 0.75 (F) 95% CI, 0.40-1.42	Ors for chronic bronchitis compare of only filter smokers to only non-filter smokers. ORs unadjusted for cigarettes per day are not adjusted for any factor. ORs adjusted for cigarettes per day are adjusted for age.
Pettiti, D. B., and Friedman, G. D., *J. Preventive Med.*, 14: 217-225, 1985	4-year prospective follow-up of 16,270 current regular smokers and 42,113 subjects who never used any form of tobacco	1979-1982		1.00 (M+F) 95% CI, 0.90-1.10	RR for COPD per 5 mg tar reduction in tar per cigarette. RR is adjusted for age, sex, and race.
Krzyanowski, M., et al., *Am. Rev. Resp. Dis.*, 143: 306-311, 1991	690 smokers from a sample of households in Tucson, Arizona, followed to 1988	1981-1988			After adjustment for intensity and duration of smoking and depth of inhalation, there was no effect of tar or nicotine on chronic phlegm, cough or dyspnea. Tar and nicotine content had no independent effect on pulmonary function.
Brown, C. A., et al., *J. Epidemiol. Community Health*, 45: 287-290, 1991	2,801 current cigarette smokers (1,154 males, 1,647 females), 40-59 years of age, from 22 districts of Scotland (Scottish Heart Health Study): cross–sectional random sample.	1984-1986			Rates of chronic cough and chronic phlegm were lower for women who smoked low-tar cigarettes, but not for men.

Citation	Population	Time Period	RR or OR Unadjusted for Cigts./Day	RR or OR Adjusted for Cigts./Day	Remarks
Withey, C. H., et al., *J. Epidemiol. Community Health*, 46: 281-285, 1992	Intervention trial in 21 local authority districts in England; male middle-tar smokers aged 18-44 years; 1,541 smokers selected from 265,016 sent questionnaires; 643 controls	1985-1989			No difference in respiratory symptoms with switching to different types of cigarettes.

a. Reference provided in Chapter 4 is to the review by Lee, as opposed to the original article by Hammond, et al.
b. Relative risk of 0.78 listed in Table 10 is based on a comparison of a tar reduction of 15 mg, while the relative risk listed in Table 4-3 of Chapter 4 of 0.94 is based on a comparison of filter vs. non-filter. See text for further discussion.

focus on a RR that is based on a known reduction of tar rather than one that is based than on the more imprecise comparison of filter to non-filter in order to truly assess the association of tar reduction on risk of chronic obstructive pulmonary disease mortality. Therefore, it would be more accurate to state that of the four studies that investigated the association of tar reduction with chronic respiratory mortality, two of them demonstrated a risk reduction, whereas two of them did not.

The reason that calculated meta-analysis shows a 30% statistically significant risk reduction can be attributed to the inclusion of three studies (Dean, et al., 1977; Hawthorne and Fry, 1978; and Alderson, et al., 1985) that focused only on chronic bronchitis. All three of these studies showed substantial decrease in risk for chronic bronchitis. Although chronic bronchitis is clearly included within the umbrella of chronic respiratory disease and is clearly associated with smoking, it is not impossible that reduction in cigarette tar yield could demonstrate a more striking reduction in risk for chronic bronchitis than for chronic obstructive pulmonary disease. However, it should be noted that in the text of Chapter 4, only the Alderson, et al. (1985) study is mentioned, and that study only briefly.

Burns, et al., devote a fair amount of discussion to the three studies listed in Table 10 (and Table 4-3) that focus on respiratory symptoms (Krzyanowski, et al., 1991; Brown, et al., 1991; Withey, et al., 1992). These studies provide little evidence that, under the experimental design used by these authors, there was a reduction in respiratory symptoms related to lower delivery cigarettes. However, in that these are not strictly epidemiological studies, in that no measurable decrease (or increase) in risk can be determined from the data, these results cannot be included in any meta-analysis.

The following conclusions would seem to be warranted: (i) there is some evidence for reduction of chronic obstructive pulmonary disease/emphysema associated with reduction in cigarette tar delivery; (ii) there is reasonable evidence for reduction of chronic bronchitis associated with reduction in cigarette tar delivery; and (iii) there is equivocal evidence for a reduced rate of respiratory symptoms. It must be noted, however, that given the paucity of the data, these conclusions must be regarded as tentative.

J. Summary of the Epidemiological Evidence

This short section – two paragraphs – summarizes the epidemiological data without adding any significant information. The first paragraph concludes that:

> "...it is difficult to conclude from these data that there is clearly demonstrable harm reduction that is due to the use of filtered or lower yield cigarettes in comparison to unfiltered or higher yield cigarettes."

This evidence that Burns, et al., use to support this conclusion is completely out of line with appropriate interpretation of epidemiological results. Burns, et al., first state that "[S]tudies in the epidemiological literature support a difference in lung cancer and possibly heart disease risks..." They then attempt to disregard these studies as follows. First they point out that there is marked variability among the studies. They point out that many studies find no effect or an effect too small to be statistically significant. In addition they state that in some studies heart disease and lung cancer risks appeared in opposite directions with low-yield cigarettes, as did risks for male and female smokers. Factually, these observations are quite correct. However, these observations can be made with respect to any set of epidemiological data regarding weak associations. An excellent example are epidemiological studies that have provided data on the association of ETS exposure and lung cancer. Some ETS/lung cancer studies have found no effect, and many have found effects too small to be statistically significant. Moreover there are examples of studies with opposite results for males and females. However, it is the meta-analytic relative risk (see, e.g., US EPA, 1992, Hackshaw, et al., 1997), which is less than the meta-analytical risk found for the

association of reduced tar with reduction of lung cancer risk and approximately equal to that for reduction of cardiovascular risk, that has convinced virtually every public health group to take the viewpoint that the ETS exposure is causally related to lung cancer. One must ask why did the authors of Chapter 4 not calculate a meta-analytical relative risk for reduction in lung cancer and cardiovascular risk associated with tar reduction. Burns, et al., also mention, once again, that adjustment for cigarettes per day could be responsible for a risk reduction being observed, without a true risk reduction occurring, if smokers of lower tar delivery or filtered cigarettes increased their consumption. Once again, this hypothesis is testable, and has been shown not to be the case. Lastly, the authors point out the possibility of confounding factors. Potential confounding is always a legitimate concern when investigating weak associations, and there is clearly insufficient data to rule out confounding. On the other hand there are no data that support confounding, and the fact that a number of key Bradford Hill aspects support a causal relationship between tar reduction and risk for disease in smokers, at least for lung cancer, somewhat minimizes the concern regarding confounding. In short, it is modern epidemiological practice, when dealing with a large number of epidemiological studies, to summarize results as best as possible using meta-analysis, and to determine from a heterogeneity analysis whether there are factors that suggest that meta-analytic treatment of the data is inappropriate. Chapter 4 has failed to take this approach. When such an approach is taken, the conclusions from the epidemiological data are quite different from the conclusions presented in this section.

Burns, et al., would appear to cite some support for their opinions in the last paragraph of this section, reproduced completely below:

> "These epidemiological data were also recently reviewed by the Tobacco Advisory Group of the Royal College of Physicians (2000) in conjunction with the evidence for compensation in smoking behavior with use of low-yield brands. They concluded, 'There are therefore reasonable grounds for concern that low-tar cigarettes offer smokers an apparently healthier option while providing little if any true benefit'."

This report is not among the references listed for Chapter 13. The only reference to the Royal College of Physicians is a report published in 1962. Moreover, we have been able to find anyone who knows of this report. Obviously, we will continue looking.

K. Biologic Implications of Compensation for Changes in Cigarette Design

This section, as the title suggests, briefly discusses possible biological explanations as to why active smoking of filter cigarettes could be more hazardous than predicted simply on the basis of tar yield. The majority of this section is devoted to a discussion of differences in smoke aerosol particle diameters between filter and non-filter cigarettes. This topic is beyond the scope of this review. However, it would appear that no conclusions are reached. This is because although there are data that suggest that smoke particles from filtered cigarettes have an average particle diameter slightly smaller than smoke particles from a non-filtered cigarette (0.84 μ compared to 0.94 μ), the chapter then goes on to state that for cigarettes with a ventilated filter this difference disappears.

The section concludes with a brief discussion of filter cigarettes and adenocarcinoma that is within the scope of this review. Burns, et al., make the statement that:

> "Changes in pattern of deposition of smoke aerosol have been postulated (Thun, et al., 1997) as one mechanism underlying the dramatic increase in adenocaricnoma (a cancer felt to arise from the more peripheral structures of the lung) seen over the last several decades (Travis, et al., 1995) in the United States and other countries (Russo, et al., 1997; Levi, et al., 1997)."

First, it is extremely important to point out that it is quite likely that there has been no "dramatic increase in adenocarcinoma" over the last several decades, but rather than the observed temporal change has been an increase in adenocarcinoma as a total percentage of lung cancer incidence or mortality. In countries, such as the US, where lung cancer (in males) is declining, both adenocarcinoma and squamous cell carcinoma are declining. However, squamous cell carcinoma is declining at a significantly more rapid rate than is adenocarcinoma (Thun, et al., 1997). Secondly, the vast majority of the evidence that the change in the distribution of lung cancer is associated with the increase in the use of filter cigarettes is a temporal correlation; that is, both the rapid growth of market share of filter cigarettes and the relative increase in adenocarcinoma occurred over the same period of time. There is another change that is equally temporally correlated; namely, the increase in the percentage of lung cancer cases that occur in ex-smokers. There is considerable data showing that adenocarcinoma is considerably more prevalent in ex-smokers than in current smokers (Khuder and Mutgi, 2001). However, this explanation is, at least at present, equally speculative.

Burns, et al., go on to state:

> "An additional concern has been increases in the levels of tobacco specific nitrosamines in cigarettes over time, particularly NNK, which is a potent lung carcinogen for adenocarcinoma in animals (Hecht, 1998; see Chapter 5)...Increased levels of tobacco-specific nitrosamines have the potential to make cigarettes manufactured after the 1960s more carcinogenic and may have contributed to the rise in adenocarcinoma, which has become the most common form of lung cancer."

There are certainly data that confirm that, as Burns, et al., point out, changes in US curing practices have led to an increase in the tobacco specific nitrosamine level in bright tobacco. However, these changes are unique to the US. In that the relative increase in adenocarcinoma has been observed in nearly 20 different countries (see, e.g., Russo, et al., 1997; Levi, et al., 1997), the tobacco specific nitrosamine theory cannot be regarded as being tenable to explain temporal trends in adenocarcinoma.

L. Correlation of Cigarette Brand Choice with Number of Cigarettes Smoked per Day and Duration of Smoking

This section discusses a number of factors that could influence the number of cigarettes smoked per day as a function of the tar level of the brand smoked. It fails to reach any conclusions in that the factors discussed are often contradictory. For example, it points out that a smoker of a lower tar cigarette may need to smoke more cigarettes in order to obtain the same amount of nicotine that would be obtained from higher tar cigarettes. On the other hand it states that a highly addicted smoker may not be able to obtain sufficient nicotine from lower delivery cigarettes. Therefore, individuals smoking lower delivery cigarettes may be less addicted, require less nicotine, and therefore smoke fewer cigarettes a day.

The section ends with references to studies by Benowitz, et al., (1983) and Jarvis (2001) showing only a weak correlation between machine-measured tar delivery and nicotine yield. Although critiques may be made of both studies, neither study is at all relevant to the issues at hand. As Burns, et al., have already pointed out, the only type of compensatory behavior that could change the measured epidemiological results would be an increase in cigarettes per day. This review has demonstrated that adjusting for cigarettes per day does not change the epidemiological results. Burns, et al., instead of carrying out such an analysis themselves, attempt to use indirect evidence in the next two sections to try and demonstrate that there is a increase in cigarettes per day smoked by smokers of lower delivery cigarettes.

M. Changes in Number of Cigarettes Smoked per Day with Differences in Machine-Measured Nicotine Yields in the American Cancer Society's Cancer Prevention Study I

This section focuses, once again, on an analysis of CPS-I data with the goal of demonstrating that the observed reduction in lung cancer RR that was published by Hammond, et al. (1976), adjusted for cigarettes per day, would disappear if the data had not been adjusted for cigarettes per day. As has been pointed out in our discussion (Section F) of the CPS-I study, data are presented that clearly allow for calculation of lung cancer RR unadjusted for cigarettes per day. Also, as we pointed out in Section F, although the publication by Hammond, et al. (1976) does not present such data, the complete data set for CPS-I is available to us, and that calculation was carried out and is shown in Section F. This calculation, reproduced below, clearly shows no evidence of a reduction in relative risk comparing the unadjusted RRs to the adjusted RRs .

Males – Low-tar vs. high-tar adjusted for cigarettes per day: RR = 0.71

Males – Low-tar vs. high-tar unadjusted for cigarettes per day: RR = 0.71

Females – Low-tar vs. high-tar adjusted for cigarettes per day: RR = 0.50

Females – Low-tar vs. high-tar unadjusted for cigarettes per day: RR = 0.46

For males, there was absolutely no change in the RR as a result of adjustment for cigarettes per day, while for females, the data indicate (although certainly do not prove, given the uncertainty of the data) that the lower tar smokers smoked somewhat less, since the RR unadjusted for cigarettes per day was actually slightly lower than the adjusted RR.

Clearly, had Burns, et al, carried out this calculation, there would have been no need for this section. Nevertheless, it is important to look closely at the conclusions Burns, et al., attempt to draw from the analyses carried out in this section.

Burns, et al., point out that earlier papers that have attempted to look at the relationship between tar level and cigarettes smoked per day for the CPS-I sample have been at best inconclusive.

> "Hammond and Garfinkel (1964) examined the first 2 years of follow-up of the CPS-I data (1959-1961). They did not demonstrate a relationship between an increased, decreased, or unchanged tar and nicotine yield of the cigarettes smoked and a change in the categorical measure of number of cigarettes smoked per day. In an analysis that examined change over the 12-year follow-up of the CPS-I data, and which examined continuous as opposed to categorical measures of numbers of cigarettes smoked per day, Garfinkel (1979,1980) showed a modest difference between increasing tar and nicotine yield of the cigarettes smoked and decreased numbers of cigarettes smoked per day, particularly for females, but the effect was small."

Burns, et al., have re-examined the relationship between nicotine yield of the cigarette smoked and the number of cigarettes smoked per day for white males within the CPS-I population. In Figure 4-6 they show a graphical representation that plots mean adjusted cigarettes per day vs. machine-measured nicotine yield per cigarette (FTC method) for all white male smokers (N=169,610) that indicates an increase of 0.8 cigarettes per day for a 1 mg decline in nicotine. The high- and the low-tar category that Hammond, et al., (1976) utilized for their comparison (see Table 2A) was 25.8-35.7 mg tar for the high-tar cigarettes and <17.6 mg tar for the low-tar cigarettes. If we take the midpoint of the range for high-tar; i.e. 31 mg tar/cigarettes, and a conservative estimate for the average low-tar cigarettes, i.e. 15 mg tar/cigarette, there is an average difference of 16 mg tar between the two groups. This translates into an average difference of 1.6 mg nicotine, or an increase in cigarettes per day between the two groups of 1.4

cigarettes per day. Such an increase is indeed possible. We will examine whether correcting for this increase could account for the observed reduction in relative risk for lung cancer, using conclusions that Burns, et al., advance, at the end of this section.

Burns, et al., then proceed to limit their analysis to "those who had changed the brand of cigarettes that they reported smoking in sequential follow-up surveys." When this analysis was carried out, shown graphically in Figure 4-7, the increase in cigarettes per day for each mg decline in nicotine was 2.31 cigarettes per day, compared to the 0.8 cigarettes per day when the total sample of white males. This analysis is completely irrelevant. First of all, Burns, et al., never discuss the size of this sample. The legend of Figure 4-7 states that N = 169,610, which was indicated in Figure 4-6 to be the total sample of white male smokers in CPS-I. More importantly, however, Hammond, et al., report lung cancer RR values for the entire sample of white males, not the group of white males that changed the brand of cigarettes that they reported smoking in sequential follow-up surveys. If this subgroup had an increase of 2.31 cigarettes per day, then the remainder of the sample forcibly would have had an increase of cigarettes of somewhat less than 0.8 cigarettes per day in order for the average of the entire sample of white males to be 0.8 cigarettes per day. Since no indication of the size of the group that switched brands was provided, it is impossible to even estimate the increase (or even decrease) in cigarettes per day for the remainder of the sample.

In Figure 4-8 Burns, et al., present the relationship between cigarettes smoked per day and lung cancer excess death rate for all CPS-I smokers of high-tar and low-tar cigarettes (as defined by Hammond, et al.). This graph shows an increase in excess lung cancer death rate as a function of cigarettes per day smoked. That lung cancer risk increases as a function of cigarettes per day has been shown in virtually every epidemiological study that has investigated active smoking and lung cancer; therefore, this result is hardly surprising. This graph also demonstrates that at any given cigarette per day value, the excess lung cancer death rate is less for the low-tar category than the high-tar category. For example, at 20 cigarettes per day the rate per 100,000 of excess lung cancer deaths is about 160 for the high-tar category and about 120 for the low-tar category, or a difference of 40 excess deaths per 100,000. This translates into a reduction in relative risk of about 25%, which is almost exactly the relative risk decrease reported by Hammond, et al. Graphically, Burns, et al., demonstrate that for a decrease in RR adjusted for cigarettes per day, a change in 4 cigarettes per day would be sufficient to eliminate any difference in RR between the high-tar and low-tar categories if the results were not adjusted for cigarettes per day. According to their calculations, the difference in nicotine levels between the high-tar group and the low-tar group was 1.33 mg. As can be seen from above, this review actually suggested a more conservative difference of 1.6 mg nicotine between the high-tar category and low-tar category. Burns, et al., then use the analysis for brand switchers that suggested an increase in 2.31 cigarettes day for each mg decline in nicotine to determine that this group had increased the number of cigarettes per day, in moving from high-tar to low-tar, of 2.31 times 1.33 or 2.79 cigarettes per day. Based on Figure 4-8 this would explain approximately 2.31/4 or about 62% of the observed decrease in lung cancer risk reported by Hammond et al. They therefore conclude:

> "The magnitude of this upward compensation, if it occurred across the entire population using lower yield cigarettes in the CPS-I, is large enough to explain much of the reduction in lung cancer risks found among low yield cigarette smokers."

This conclusion is completely unwarranted for two main reasons:

1. The upward compensation Burns, et al., used cannot have occurred across the entire population. Data from CPS-I were already presented demonstrating that the increase in cigarettes per day for the entire population was 0.8 per mg nicotine comparing smokers of low-tar cigarettes to smokers of high-tar cigarettes. As previously indicated, this would translate into a 0.8 times 1.33, or 1.06 cigarette per day increase between the high-tar and low-tar groups. This would explain approximately only 25% of the decrease in lung cancer risk.

2. The analysis of Burns, et al., is at best a rough approximation. Not only does it rest on a number of approximations, but simply because a given smoker increases the number of cigarettes per day does not mean that other changes in smoking behavior could not occur to eliminate any increased risk that might accrue from increasing cigarettes per day. Where possible, the only meaningful method to test the effect of a potential increase in cigarettes per day is to compare the results unadjusted and adjusted for cigarettes per day. This calculation was clearly possible for Burns, et al., to have carried out using CPS-I data. As we have shown, this calculation clearly demonstrates absolutely no increase in lung cancer risk for low-tar smokers when the unadjusted RR is compared to the adjusted RR.

N. Number of Cigarettes Smoked per Day among Smokers of Cigarettes with Different Machine-Measured Nicotine Yields for Current Cigarettes – California Data

This section, the last section that explicitly discusses the effect that increased cigarettes per day could have on the observed decrease in epidemiological relative risk for lung cancer for smokers of filter (or low-tar) cigarettes compared to non-filter (or high-tar) cigarettes utilizes data taken from two California Tobacco Surveys (1990 and 1996). (Although we have been able to obtain a number of reports from the California Tobacco Survey, we have been unable to find one or more Reports that contain the data discussed in this section. Moreover, there is no reference to any of these Reports in the list of references at the end of Chapter 4. It is clear from the legends of the figures that data exist that give average cigarette per day figures for each brand of cigarettes smoked in California. Nicotine levels of these cigarettes were obtained from Maxwell Report data for 1990 and from the tobacco companies themselves in 1996.) The results of this discussion are portrayed graphically in Figure 4-11, which plots cigarette nicotine level against reported cigarettes smoked per day. The result is that there is a relatively constant relationship between nicotine level and cigarettes smoked per day within the range of 1.75 mg nicotine per cigarette to about 0.95 mg nicotine per cigarette. For cigarettes delivering less than 0.95 mg nicotine, there is a constant increase in cigarettes smoked per day up to the lowest level of nicotine recorded (0.15 mg nicotine per cigarette) with the number of cigarettes smoked per day increasing from about 29 to 37, or an increase of 8 cigarettes per day.

Without being able to access the raw data that were used to construct this table, it would be most difficult to question their accuracy. Therefore, this review must assume that they are accurate. However, although the data may be accurate, they are of at best limited relevance. Cigarettes that deliver 0.95 mg nicotine, deliver about 10 mg tar. Therefore, the tar range over which the observed increase in cigarettes per day occurs is from about 1 to 10 mg tar per cigarette. Many of the epidemiological studies that have been conducted precede the introduction of cigarettes with less than 10 mg tar; as a consequence, results from these studies would clearly not be able to be evaluate the relevance of the California Tobacco Survey data. Those studies that are relevant are presented in Table 11, a subset of the studies listed in Table 2.

It is immediately obvious from Table 11 that there are insufficient data with respect to lung cancer risk for cigarettes below 10 mg tar. Only two studies (Sidney, et al., 1993; Wilcox, et al., 1988) allow a comparison of adjusted and unadjusted RRs, and no conclusions can be drawn from these two studies. Until further data are generated regarding this category of cigarettes, it cannot be determined if the purported increase in cigarettes per day for cigarettes of 10 mg tar or less actually affects any apparent reduction in lung cancer risk for smokers of these cigarettes.

Table 11 RR for Low-Tar Smokers Compared to High-Tar Smokers Where the Low-Tar Category is Less Than About 10 mg Tar					
Study	**Time Period**	**Reference Group, Comparison Group**	**Cases**	**RR (OR) Unadjusted for Cigts./Day**	**RR (OR) Adjusted for Cigts./Day**
Wynder and Kabat, 1988	1977-1984	>14, <10 mg tar	682 (M) 492 (F)	1.32 (M) 0.93 (F)	
Sidney, et al., 1993	1979-1985	>18, <11 mg tar	82 (M) 76 (F)	0.92 (M) 1.48 (F)	0.79 (M) 1.49 (F)
Wilcox, et al., 1988	1980-1981	21-28, <10 mg tar	373 (M)	0.53 (M)	0.61 (M)
Garfinkel and Stellman, 1988	1982-1986	>20, <5 mg tar	570 (F)		0.63 (F)

The need for sound epidemiological data to assess the potential role of increasing cigarette consumption over the tar range of 1 to 10 mg tar per cigarette can be seen if one looks at the data from the California Tobacco Survey in a somewhat different manner. First, there is no question that lung cancer relative risk is related to dose in a roughly linear manner. Therefore, if there were no compensation of any type, the relative risk for a smoker of a 1 mg tar cigarettes compared to a smoker of an equivalent number of 10 mg cigarettes would be 0.1. Now let us assume that through various types of compensatory behavior (more frequent puffs, deeper puffs, vent blocking, etc.) that the 1 mg smoker, actually receives 5 mg tar from each cigarette, as opposed to 1 mg per cigarette. For an equivalent number of cigarettes the 1 mg smoker would now have a relative risk of 0.5 compared to the 10 mg tar cigarette smoker. Lastly, let us now assume, based on the data presented by Burns, et al., that the smoker of the 1 mg tar cigarette smokes 37 cigarettes per day, while the smoker of a 10 mg tar cigarette smokes only 29 cigarettes per day. The total actual exposure to tar for the 1 mg smoker is 5 mg tar per cigarette times 37 cigarettes per day or 185 mg tar, compared to 10 mg tar per cigarette times 29 cigarettes per day or 290 mg tar. This still results in a relative risk for the 1 mg tar smoker of 185/290 or 0.64. This 36% reduction in lung cancer risk is still considerable. This brief analysis once again points to the conclusion that until sound data on very low-tar cigarettes are generated, it is impossible to assess the effect of a possible increase in cigarettes per day for smokers of such cigarettes.

This section is the last section of Chapter 4 that deals with the issue of the effect of increased cigarettes per day on the observed lung cancer risk for smokers of cigarettes with reduced machine-measured tar yields. The authors arrive at no final conclusions, and indeed, in the opinion of this review, no final conclusions that suggest that increase in cigarettes per day can explain the observed epidemiological decrease in risk are warranted. The conclusions of this review are as follows:

1. Epidemiological studies show a clear picture of a reduction in lung cancer risk and a lesser, although still statistically significant, reduction in risk for cardiovascular disease risk for smokers of filter (or low-tar) cigarettes compared to smokers of non-filter (or high-tar) cigarettes.
2. Analysis of the epidemiological data demonstrates no difference, as a function of adjustment for cigarettes per day, in pooled relative risk comparing either smokers of filter cigarettes to smokers of non-filter cigarettes or smokers of low-tar cigarettes compared to smokers of high-tar cigarettes.

3. Burns, et al., present two different analyses of CPS-I data in order to demonstrate that smokers of lower tar cigarettes had smoked more cigarettes per day than smokers of higher tar cigarettes. These analyses are completely irrelevant, since a comparison of reduction of relative risk for lung cancer from CPS-I shows no difference in relative risk adjusted or not adjusted for cigarettes per day.
4. Burns, et al., present recent data from the California Tobacco Survey indicating an increase in cigarettes per day over the range of 1-10 mg tar delivery per cigarette. Although there are insufficient data to evaluate the possible effect that such an increase might have, it can be easily demonstrated that it would not be sufficient to eliminate a decrease in lung cancer relative risk for smokers of very low delivery cigarettes.

O. Temporal Trends in Lung Cancer and Other Diseases in Major Cohort Studies

This section discusses two "major prospective mortality studies of smoking and disease" that "bridged the period of greatest reduction in tar levels of cigarettes." These two studies are the British Physicians Study and the two American Cancer Society Studies, CPS-I and CPS-II. These two studies are actually quite different.

The British Physicians Study (Doll, et al., 1994) examined lung cancer mortality rates with a follow-up period of over 40 years. The follow-up interval was divided into two 20-year periods, 1951-1971 and 1971-1991. Age-standardized lung cancer death rates in males smokers increased by 19% to 314 per 100,000 during the second half of the study compared to 264 per 100,000 during the first 20 years of follow-up. This increase occurred during a period when the tar level of cigarettes in the United Kingdom had fallen dramatically.

The British Physicians Study followed the same cohort prospectively over the entire 40-year follow-up period. It is a reasonably safe assumption that the vast majority of this cohort were smoking non-filtered cigarettes when follow-up was initiated. Unfortunately, data are not presented that provide a smoking history for the cohort. Nevertheless, given the fact that many smokers are extremely brand loyal, it is highly likely that a much larger percentage of this cohort continued to smoke non-filter cigarettes than did the population in general. As Burns, et al., point out themselves (p. 67):

> "Limitations of following a single cohort for long periods of follow-up include the fact that the cohort becomes less and less representative of the entire population over time, and, in particular, it is limited in its ability to examine the effects of changing cigarette design on smokers who initiate with those products rather than switched to them."

Secondly, although lung cancer rates are age-standardized, no adjustment has been made for either changes in smoking intensity (cigarettes per day) or in duration of smoking. This point is acknowledged by Burns, et al. Therefore, it is highly likely that the relatively modest increase in age-adjusted lung cancer death rates observed for the second 20-year follow-up of the British Physicians Study cohort could be fully explained through a more detailed analysis of this cohort. As indicated, the required data are not available to make such an analysis.

The situation is quite different for the two American Cancer Society Studies, CPS-I and CPS-II. These two studies, initiated 23 years apart (CPS-I was initiated in 1959 and CPS-II, in 1982), selected a new cohort for follow-up at the beginning of each study. Therefore, each cohort was reasonably representative of the US population during the period of selection. (We say "reasonably representative," since the method by which the cohorts were selected – volunteers from the American Cancer Society interviewing friends and relatives – was not designed to select a population that truly represented the total US population. The two cohorts were under-represented in, for example, blacks, Hispanics, and individuals in the lower socioeconomic strata. However, this slight flaw certainly does not affect a comparison between the two studies, since the

same procedures were used to select both cohorts. Moreover, the results discussed in this review are consistent with data taken from the US population as a whole.)

Burns, et al., point out that there was a substantial increase in lung cancer death rates in CPS-II compared to CPS-I during a 6-year follow-up period. Although not stated, the increase in lung cancer death rates for males was about 2, whereas for females, the increase in lung cancer death rates was about 5. Adjustment for differences in smoking intensity and smoking duration reduces the difference for both males and females by a factor of 2. However, the increase in lung cancer death rates for CPS-II compared to CPS-I is still substantial, particularly for women.

Burns, et al., present some data in graph form comparing the two studies. They conclude:

> "However, the comparisons do not suggest that even filter smokers in CPS-II had any reduction in lung cancer risk when compared to smokers in CPS-I more than 20 years earlier. Some of this increase in lung cancer risk between the two studies may have resulted from greater availability of cigarettes and resultant heavier smoking among adolescents during the period when smokers in CPS-II were initiating their smoking behaviors. Alternatively, increased depth of inhalation with lower yield cigarettes and higher levels of tobacco-specific nitrosamines in the tobacco used in more recent cigarettes (see Chapter 5) may also have contributed to the increase. But detailed examination of the risks in these two studies separated by over 20 years does not suggest a reduction in risk resulting from lower yield cigarettes."

Before commenting further on the differences between CPS-I and CPS-II it is important to note that Burns, et al., fail to point out that a direct comparison between filter smokers and non-filter smokers in both CPS-I and CPS-II show a decreased relative risk for lung cancer for filter smokers. Moreover, the relative risks are not increased when comparing unadjusted RRs to adjusted RRs for both studies, but rather somewhat decreased. This suggests that the filter smokers may have actually been smoking fewer cigarettes per day. The results from the first 6 years of follow-up from CPS-I are as follows:

Males – Filter vs. non-filter adjusted for cigarettes per day: RR = 0.92

Males – Filter vs. non-filter unadjusted for cigarettes per day: RR = 0.90

Females – Filter vs. non-filter adjusted for cigarettes per day: RR = 0.48

Females – Filter vs. non-filter unadjusted for cigarettes per day: RR = 0.44

Results from the 6-year follow-up period of CPS-II are as follows:

Males – Filter vs. non-filter adjusted for cigarettes per day: RR = 0.79

Males – Filter vs. non-filter unadjusted for cigarettes per day: RR = 0.81

Females – Filter vs. non-filter adjusted for cigarettes per day: RR = 0.79

Females – Filter vs. non-filter unadjusted for cigarettes per day: RR = 0.75

Clearly, as the above data demonstrate, both CPS-I and CPS-II confirm a reduced relative risk for lung cancer for filter smokers compared to non-filter smokers. Therefore, can one actually state that "detailed examination of the risks in these two studies separated by over 20 years does not suggest a reduction in risk resulting from lower yield cigarettes"?

Before attempting to answer that question, it is necessary to summarize our internal analyses of the comparison of CPS-II and CPS-I. Our results are in complete agreement with the fact that age-adjusted lung cancer rates increased in CPS-I compared to CPS-II. As indicated, after adjustment for smoking intensity and duration, we find a 50% increase in age-adjusted relative risk for males and a 150% increase for females. An extremely large group of potential confounders were examined to determine if any of them could account for the differences between the two studies. No significant confounding effect was found. Moreover, the increase of CPS-II compared to CPS-I was evident in every category of smoking intensity. There is, therefore, no question that in the 20-year period between CPS-I and CPS-II there was an apparent increase in lung cancer relative risk. Moreover, when these results are examined in light of other studies, which will be discussed in the next sections, there is little doubt that this increase in US lung cancer relative risk and incidence rates is quite real. However, given the fact that in both studies relative risks for lung cancer rates are reduced for smokers of filter cigarettes, it seems highly unlikely that this increase in US lung cancer rates was because of the introduction of lower yield cigarettes in the US.

As can be seen, the increase in lung cancer risk for smokers in CPS-II compared to CPS-I clearly reflects an increase in lung cancer incidence and mortality in the US that has been documented by several investigators. The risk for non-filter cigarette smokers increased, and the risk for filter cigarette smokers increased. Given this, why might Burns, et al., claim that this observed increase "does not suggest a reduction in risk resulting from lower yield cigarettes?" The only possible reason that this review can advance is that the percentage of filter smokers is clearly significantly greater in CPS-II than it was in CPS-I. Therefore, because of this increase in percentage of filter cigarette smokers, wouldn't one have expected to see a decrease in lung cancer risk, if the lung cancer risk for filter cigarette smokers is truly less than for non-filter cigarette smokers? That this would actually not be the case can be shown through a simple calculation. Let us assume that the relative risk for white male never smokers, filter smokers and non-filter smokers were 1, 8, and 10 for CPS-I. These relative risks reflect the actual situation within CPS-I relatively accurately. Let us further assume that the relative risks for white male never smokers, filter smokers and non-filter smokers were 1, 16 and 20 for smokers in CPS-II. Therefore, the relative risks have doubled for both filter and non-filter smokers between CPS-II and CPS-I, the risk for non-smokers has remained the same, and the risk for filter smokers is about 20% less than the risk for non-filter smokers. Again, these figures represent the actual situation within CPS-II relatively accurately. Let us further assume that there were 25% filter smokers within CPS-I, and 75% filter smokers within CPS-II. Then the weighted relative risk for all white male smokers in CPS-I would have been 9.5 ([0.75x10 + 0.25x8]/2), while the relative risk for all white male smokers in CPS-II would have been 17 ([0.25x10 + 0.75x16)/2). The comparative relative risks for all white male smokers for CPS-II and CPS-I would then be 17/9.5 or 1.79. Therefore, even correcting for the much greater percentage of filter cigarette smokers in CPS-II leads to a very substantial increase between the two studies. In other words, the increase is relatively insensitive to the population change of filter and non-filter smokers. Carrying out an actual analysis would be possible; however, it would be complicated by the fact that many filter smokers in CPS-II would have had a long history of smoking non-filter cigarettes before switching. Therefore, the above analysis can considered to be a more than adequate model.

Published reports that first discussed the unexpected increase in lung cancer risk for CPS-II compared to CPS-I do not appear to draw the same conclusion that Chapter 4 does. For example, in the discussion of the comparison of these two studies, Thun and Heath (1997) point out several possible explanations for the significant increase in lung cancer rates in the US as demonstrated by CPS-I and CPS-II. These explanations include changing demographic patterns of smokers, decrease in starting age of smokers, and possible changes in the inherent hazards of US cigarettes. As a matter of fact Thun and Heath (1997) state that:

> "First, although the sharp increase in lung cancer death rates from CPS-I to CPS-II is clearly an adverse consequence of cigarette smoking, we cannot tell whether lung cancer risk might not have increased even more but for the reduced tar yield in cigarettes."

There is another possible explanation for the increase in US lung cancer rates seen between 1960 and 1980; namely, that some life style characteristic of the US population that acts as an effect modifier for lung cancer could have increased over that period. Such an effect modifier could be diet, lack of exercise or perhaps another factor. However, at present all of these possibilities are speculative at best.

What is known, however, is the following:

1. Lung cancer relative risks associated with smoking increased significantly between 1960 and 1980, and this increase is reflected by the results of CPS-II and CPS-I.
2. In both CPS-I and CPS-II there was a reduced relative risk for filter smokers compared to non-filter smokers, and this difference in relative risk does not disappear when adjustment is not made for cigarettes per day.
3. The observed increase does not provide any meaningful information regarding the comparative lung cancer risk for smokers of filter cigarettes compared to smokers of non-filter cigarettes.

P. Temporal Trends in National Lung Cancer Death Rates and Smoking Behaviors

This single paragraph serves as an introduction to a rather detailed discussion in the next, and last, four sections. Burns, et al., state that:

> "The ultimate measure of a benefit from any reduction in the risk of smoking is a change in national death rates. Lung cancer death rates in both the United States and United Kingdom have declined among males in recent years. Several investigators have examined the relationships between smoking behaviors and changes in lung cancer mortality in both countries, and these analyses are now considered in relation to trends in tar yields of the cigarettes smoked in both countries."

Q. Published Models Using Smoking Behavior to Predict National Lung Cancer Death Rates

This section is primarily devoted to a brief discussion of various models that have been published, generally known as multi-stage models, that attempt to predict lung cancer rates based on cigarettes smoked per day and smoking duration. The best known of these models, and the first that Burns, et al., discuss, is the Doll and Peto model (1978). This model can be stated explicitly as:

$$\text{Lung Cancer Incidence} = 0.273(\text{cigarettes/day} + 6)^2(\text{age}-22.5)^{4.5}$$

It is important to note that the form of the model used by Doll and Peto is only applicable when applied to a population that initiated smoking at about the same time. Age, in the above model, serves as a surrogate for duration of smoking, and this surrogate is valid only if age at start is relatively constant. It is also important to note, although it is not germane to this review, that this model is applicable only to smokers. Doll and Peto, as well as others, have also developed a model for non-smokers, which, of course, does not contain a term for cigarettes per day. However, lung cancer incidence in non-smokers is related exponentially to age. Doll and Peto propose a relationship of lung cancer incidence to age to the fourth power for non-smokers, meaning that relative risks of lung cancer for smokers would increase slightly compared to non-smokers. However, different investigators have published different results, leading to either no increase in relative risk (past a certain age) or an actual decline in relative risk (past a certain age).

Burns, et al., discuss briefly a number of similar models that have been published; however, this discussion is for informational purposes only. The real point of this section is not reached until the

last two paragraphs. In the next to the last paragraph, a study by Mannino, et al. (2001) is mentioned. This very recent study examined age- and birth-cohort-specific US lung cancer death rates for white males and white females, adjusting for age- and birth-cohort specific differences in prevalence and duration of smoking. This analysis confirms the findings of the comparative analysis of CPS-I and CPS-II; namely, that lung cancer mortality in the US has increased in the past several decades. Burns, et al., cite Mannino, et al., as follows:

> "Differences in lung cancer death rates across birth cohorts of U.S. men and women primarily reflect differences in the prevalence and duration of smoking. Changes in cigarette design that have greatly reduced tar yields have a relatively small effect compared with that of people's smoking status and duration of smoking."

This statement is somewhat misleading. The fact that an increase, as opposed to a decrease, in lung cancer mortality occurred during the period when sales-weighted tar yields were declining in the US cannot by itself be taken as establishing that "changes in cigarette design that have greatly reduced tar yields have a relatively small effect." As Thun and Heath (1997) pointed out, there are other explanations for the observed increase in lung cancer mortality in the US. One question that must be raised is, do experiences in other countries mirror that of the US, or are they different? Burns, et al., briefly refer to a study that reflects on the situation in the UK. This study by Peto,et al., (2000) suggests that "younger males had declines in age-specific lung cancer death rates over time that were much larger than those in smoking prevalence." Burns, et al., point out that reduction in lung cancer risk from smoking low-yield cigarettes was suggested as an explanation for this observation. No further description of this study is provided by Burns, et al. Since it appears to arrive at a conclusion far different than that drawn from the US situation, a brief description of this study is warranted.

The Peto, et al. (2001) study compared lung cancer mortality rates from two large case-control studies carried out in the UK 40 years apart (ca. 1950 and ca. 1990). Lung cancer incidence (and relative risk) in the UK had decreased considerably over this period of time. For most population subgroups investigated this decrease was completely explainable by changes in smoking prevalence and intensity over this period of time. The authors do point out, however, that for males in the 35-54 age group, mortality decreased more rapidly than did smoking prevalence. Over this period of time smoking prevalence in this sex and age group dropped from about 82 to 47%, whereas lung cancer mortality decreased from 52% to 19%. Therefore, in this group a 43% decrease in smoking prevalence is associated with a 63% decrease in lung cancer mortality. This suggests a decrease in smoking hazard for this group of smokers, which can only be attributable to decreases in tar yields of this period. A similar effect was not observed in either older men or women continuing smokers, since in the 1950's this group would not have had a long history of smoking, whereas in 1990 it was likely that they did have a long history of smoking. Likewise, for young women, the "effect of longer exposure (together with the effect of changes in the way women smoke cigarettes) overwhelms the lesser effect of the reduction in cigarette tar yields (and of other changes in cigarette composition) over this period." It would appear, therefore, that the UK experience provides some credible evidence to suggest an observable decrease in lung cancer mortality as a consequence of low-yield cigarettes.

Although the Peto, et al. (2000) study is the sole study that Burns, et al., refer to, it is not the only study to have found a relationship on a population level for decreased lung cancer mortality attributable to low-yield cigarettes. A second study, which Burns, et al., do not reference, is by Blizzard and Dwyer (2001) and deals with Australia. This study calculated age-specific rates of lung cancer mortality for Australian women for 5-year birth cohorts. Comparison for each cohort was made over the period 1965 to 1998 in five-year intervals. These mortality data were then compared to estimates of smoking prevalence for each five-year interval. One of the key findings of this study was that lung cancer mortality in post-1940's birth cohorts of women has been declining despite no decline in these birth cohorts in smoking prevalence. To cite the authors:

> "The declining mortality of successive post-1940's birth cohorts of women is at odds with increasing proportions of ever-smokers and the increasingly younger ages at which they commenced smoking."

Clearly, one possible explanation for this would be a decline for post-1940 birth cohorts in cigarettes smoked per day. Although these data are not available from the Australian smoking population in general, a recent Australian study cited by the authors suggests that this is not a likely explanation. The authors feel that a more likely explanation is change in cigarette design; that is, continuing decline in sales-weighted tar delivery.

As a consequence two recent studies suggest that there has been a measurable effect of low-yield cigarettes at the population level. Moreover, there is a recent paper (Jemal, et al., 2001) that provides similar evidence for the US, at least with respect to very recent population data. Discussion of this paper will be deferred to Section T. Burns, et al., however, choose to ignore this evidence and instead proceed with the next two sections, the purpose of which could be interpreted as an attempt to minimize the findings of Peto, et al. (2000).

R. Influence of Smoking Behaviors on Lung Cancer Death Rates in the United States and United Kingdom

This section concludes as follows:

> "In summary, a variety of changes in the patterns of cigarette smoking have occurred in both the United Sates and the United Kingdom, including changes in smoking initiation as well as smoking cessation. These changes may be responsible for many of the differences across time and between the countries in national lung cancer mortality rates."

As can be seen from the analysis of this section, it is certainly not at all clear exactly what Burns, et al., wanted to achieve. It might be assumed that there was concern regarding the assertion of the Peto, et al. (2000) study that reduction in UK lung cancer risks from smoking low-yield cigarettes was suggested as an explanation for the observation that lung cancer risks in young men declined significantly more rapidly than did smoking prevalence. It is even less clear as to what Burns, et al., accomplished in this section.

The section begins with the following sentence:

> "When considering a potential effect of changing cigarette design over time on national lung cancer death rates, it is necessary to control for changes in smoking prevalence and intensity over time because smoking intensity and duration are more powerful predictors of lung cancer risk in epidemiological studies than is tar yield of the cigarette smoked."

Whether or not one agrees with Burns, et al., that smoking intensity and duration are "more powerful predictors of lung cancer risk in epidemiological studies than is tar yield of the cigarette smoked," there is no question that both smoking intensity and duration are clearly extremely important predictors of lung cancer risk. No adequate assessment of the possible role of cigarette tar yield can be carried out without a good knowledge of smoking prevalence and smoking intensity.

This section points out that lung cancer death rates reached peak levels that were much higher in the United Kingdom than in the United States, particularly among males. However, this situation has changed, and lung cancer death rates in the United Kingdom are now much lower than those in the United States for both males and females. This point is clearly correct. Burns, et al., do not provide actual data to illustrate this point; however, the data exist, and are shown in Table 12 below.

No explanation is provided as to why either lung cancer death rates were at one time significantly higher in the US or as to why they are now significantly lower. One possible suggestion would be that male smokers among the older birth cohorts in the United Kingdom smoked hand-rolled cigarettes in high percentages. However, this explanation would not apply to women, for whom changes in lung cancer death rates certainly display the same temporal pattern as men, even if the differences are not quite as pronounced (see Table 12).

Table 12
US/UK Lung Cancer Death Rate Ratios

Males (Calculated from Table 4-6, p. 129 of Monograph 13)			
Age	**1950s**	**1990s**	**Ratio of Ratios**
32.5	0.452	1.846	4.08
42.5	0.466	1.185	2.54
52.5	0.461	1.329	2.88
62.5	0.468	1.266	2.70
72.5	0.488	0.991	2.03
82.5	0.698	0.867	1.24
Females (Calculated from WHO data)			
35-39	0.493	1.473	2.99
45-49	0.587	1.472	2.51
55-59	0.558	1.657	2.97
65-69	0.593	1.090	1.84
75-79	0.769	1.116	1.45

Burns, et al., then go on to point out that assessment of the possible role of low-yield cigarettes on lung cancer death rates may be better assessed by examining data for younger smokers, as opposed to older smokers, since these smokers are more likely to have begun their smoking with filtered and lower yield cigarettes and would have smoked them for a larger fraction of their smoking experience. Since younger smokers are exactly the group where Peto, et al. (2000), for men in the UK, and Blizzard and Dwyer (2001), for women in Australia, noted an apparent decrease in risk for smokers of lower yield cigarettes, this approach seems quite logical. However, it is not at all clear that Burns, et al., have looked at appropriate data for young smokers.

Burns, et al., point out that there is a difference in the rate of rise of lung cancer with age between the United States and the United Kingdom. These data are presented graphically in Chapter 4 in Figure 4-16 for two birth cohorts; the 1926-1930 birth cohort and the 1946-1950 birth cohort. Inspection of Figure 4-16 indicates minor differences between lung cancer death rates for the UK and the US at best, except at the youngest age; namely 32.5 (the center of the 30-34 age group). For this lowest age group, lung cancer rates are clearly lower in the US than in the UK for both cohorts. Burns, et al, then attempt to relate this difference to data collected in Table 4-7 that provides information for both the UK and the US regarding age at start. They claim that a greater percentage of smokers started smoking at ages 14-15 in the UK than in the US, and that this difference could account for the differences observed in lung cancer death rates for the 30-34 age group between the two countries. It is extremely difficult to interpret the data presented in Table 4-7. There are four different ages listed at time of survey. There are three different survey years listed, and data are not present for all survey years. An individual in the 1926-30 birth cohort would

have been 14 years of age sometime between 1940 and 1944. There are no data in Table 7 for this period of time. For an individual in the 1946-1950 birth cohort, and individual would have been 14 years of age some time between 1960 and 1965. There is no information in Table 7 for this period of time either. The earliest data are for 1970 in the US and 1971 in the UK. As a consequence, it would appear that the authors of Chapter 4 are basing their conclusions regarding differences on age of initiation on non-relevant data. Furthermore, there are other published data, that is birth cohort specific, suggesting that there is little difference in age of start for smokers in the US and the UK. Average age of initiation estimated from data provided by Burns, et al. (1997) for the US is 16.1 for males born between 1925 and 1929, and 16.2 for males born between 1945 and 1949. For the same time periods in the UK, average age of initiation estimated from the Health and Lifestyle Study (Cox, et al., 1987; Forey, et al., 2002) is 16.0 and 16.5. Therefore, the comparative average ages for initiation are virtually identical. It is not clear at this point as to what Burns, et al., are attempting to establish; however, in the next section we will see how Burns, et al., attempt to explain other differences between the US and the UK situation by looking at differences in age at start.

In the next paragraph Burns, et al., focus on the more rapid increase in lung cancer rates in the US than in the UK for the older age groups. Actually, inspection of Figure 4-16 demonstrates that there were no apparent differences at all for lung cancer death rates from age 42.5 through age 52.5 for the 1926-1930 birth cohort; however, the situation is quite different for the 1946-1950 birth cohort. Although the difference may not appear particularly great from Figure 4-16, this is because the ordinate is a log scale. Table 4-6 shows a lung cancer death rate of those individuals at age 52.5 in the 1946-1950 birth cohort of 66.10/100,000 for the US and 49.74/100,000 for the UK. This is a ratio of 1.33. The fact that the US had surpassed the UK in lung cancer death rates by the 1990's is well illustrated in Table 9 above (an individual in the 1946-1950 birth cohort would reach age 47.5 between 1993 and 1998). Burns, et al., comment on the fact that the reason for this difference is "less clear." They postulate that perhaps the greater rate of smoking cessation in the UK could account for the difference. Burns, et al., fail to cite a very detailed analysis of the UK situation published by Lee and Forey (1998). This paper fitted observed lung cancer trends for 1965-1985 for both sexes to multistage model predictions using smoking history data for two surveys. The modeling, which allowed for variation over time in age of starting and stopping smoking, amount smoked and tar levels clearly showed that in men aged 35-64 and women aged 35-54, lung cancer rates declined much more sharply than predicted by the model. The conclusions were not affected by sensitivity analyses allowing for variation in such factors as the choice of multistage parameters used, or the extent to which allowance for compensation was made. Indeed, if no benefit of tar reduction was assumed, the unexplained decline in lung cancer risk became greater. We must conclude, therefore, that the decrease of UK lung cancer rates compared to US lung cancer rates is indeed not clear. However, it cannot be explained by differences in smoking cessation.

In the next several paragraphs Burns, et al., return to the issue of differences between the UK and the US with respect to lung cancer death rates of young smokers. As was pointed out above, inspection of Table 4-6 shows that for the 1950-1954 and the 1955-1959 birth cohorts, the differences between the two countries invert. As a consequence it is difficult to be able to address these paragraphs since we do not know which differences he is referring to. He suggests that differences in age of starting, intensity of smoking at adolescence, and patterns of cessation could all influence observed lung cancer rates. Certainly, all of these factors can influence lung cancer death rates. However, no data are presented that allow any conclusions to be drawn.

As indicated, this section concludes with the following paragraph:

> "In summary, a variety of changes in the patterns of cigarette smoking have occurred in both the United States and the United Kingdom, including changes in smoking initiation as well as smoking cessation. These changes may be responsible for many of the

differences across time and between the countries in national lung cancer mortality rates."

Clearly changes in smoking prevalence – changes in smoking initiation as well as smoking cessation – will influence lung cancer mortality rates across time. This fact is well established. Clearly major differences have occurred in lung cancer mortality rates between the UK and the US over time as well. Burns, et al., have presented a number of speculative suggestions in order to explain such differences; however, they are simply speculations. Extremely detailed analyses of these factors have been carried out (Lee and Forey, 1998), without an obvious answer being found.

It is not at all clear at this point as to what Burns, et al., were trying to accomplish in this section. However, some of the points raised above will be returned to in the next two sections.

S. Examination of Trends Over Time in Age-Specific Lung Cancer Death Rates in the United States and United Kingdom

This section starts out with the following paragraph:

> "Age-specific lung cancer death rates in the United Kingdom have declined dramatically in the last several decades, and these reductions have exceeded the declines in smoking prevalence among the same age groups for those under age 45 (Peto, et al., 2000). One possible explanation for the more rapid decline over time in lung cancer death rates compared to trends in smoking prevalence is decreased risk from smoking lower yield cigarettes. A reduced risk from smoking lower yield products might be first evident among those who are younger because they would have had a larger proportion of their smoking experience with these lower yield cigarettes. However, as discussed in the previous section, it is important to examine other aspects of smoking behavior that could also account for changes in lung cancer rates before attributing the difference in lung cancer death rates to changes in cigarette yield."

The purpose of this section immediately becomes abundantly clear; namely, are there other possible explanations, besides low-yield cigarettes, for the findings published by Peto, et al. (2000)?

Burns, et al., use Table 4-6 to illustrate the dramatic percentage declines in male lung cancer death rates in the UK among those under 50, with particularly dramatic percentage declines under age 40. They point out that rates for those aged 40-49 declined by about two-thirds, with rates in the youngest age group declining by approximately 85%. These declines exceed the approximately 50% decline in smoking prevalence over time at these same ages as illustrated in Table 4-8.

Data presented in Chapter 4 show that less dramatic declines in lung cancer death rates among white males under age 50 have occurred in the US, as compared to the UK, and the observed declines closely match changes in smoking prevalence. Based on data presented in Table 4-9, Burns, et al., point out that at ages 35-39, lung cancer death rates fell approximately 48% from their peak in the 1931-1935 birth cohort to the 1951-1955 cohort, whereas smoking prevalence fell only 39%. However, there was also a 48% fall in the prevalence of smoking at age 12 across the same cohorts. Similarly, there was a 46% percent decline in lung cancer death rates at ages 40-44 from a peak in the 1926-1930 birth cohort to the last birth cohort (1946-1950) birth cohort where smoking prevalence data are available, with a decline in smoking prevalence of 36%. However, the decline in smoking prevalence at age 12 is also 36%. Burns, et al., point out that given the limited precision of these estimates and the difficulty in defining the exact measure of smoking behavior that should be compared, the changes in smoking behaviors across birth cohorts may well explain the changes in lung cancer death rates in the United States.

In the next two paragraphs Burns, et al., attempt to show that the marked declines in lung cancer death rate in the UK at ages 30-34 and 35-39 over sequential birth cohorts cannot be attributed to a reduction of the carcinogenicity of the cigarettes smoked. Lung cancer death rates for non-smokers in these two age groups of 1.2 per 100,000 and 1.9 per 100,000 were obtained from the CPS-I study. Burns, et al., therefore state that the observed death rates observed for UK smokers in these two age groups implies an essential elimination of a smoking effect at ages 30-34 and a near elimination of the effect at ages 35-39. Since there are data showing that in the UK approximately 90% of young smokers smoked cigarettes with 10 mg or more tar yield in 1990, and approximately one-half smoked cigarettes with yields of 15 mg tar or higher in the same year (Wald and Nicolaides-Bouman, 1991), this makes it biologically implausible that smoking low yield cigarettes would have almost no risk. They offer an alternative explanation that, "prevalence of intense smoking at very young ages has declined dramatically, following demonstration in the 1950s of increased disease risks due to smoking and the social policy changes that followed the publication of the Royal College of Physicians' report on smoking."

The major problem with the analysis that Burns, et al., summarized in the previous paragraph is that it looks at the data as an all or nothing situation. Although the statement that it is "biologically implausible" that cigarettes with reduced carcinogens would imply an "essential elimination of a smoking effect" is very likely to be true, this statement has no relevance to their being a decrease in lung cancer risk resulting from such cigarettes. The position that Burns, et al., have taken is equivalent to stating that since reduced yield cigarettes can't explain all of the observed data, it therefore doesn't explain any part of the data. The hypothesis that Burns, et al., offer; namely, less intensive smoking at an early age could, indeed, also explain a portion of the observed data. Burns, et al., continue this section by pointing out that lung cancer deaths in older males (40+ years) have declined in the UK as well:

> "Lung cancer death rates for males in the United Kingdom have also declined for ages 40-44 and ages 45-49 with each age group declining to one-third of its peak value, a proportionate reduction that exceeds the change in smoking prevalence within these age groups. Declines in lung cancer death rates among older age groups are more modest and are consistent with changes in smoking prevalence."

They then use data presented in Table 4-8, on UK cigarette consumption by age group, and in Table 4-6, which tabulates lung cancer death rates in the UK by age and birth cohort, to ostensibly look at changes in cessation and initiation that could have contributed to the greater decrease in lung cancer death rates for males of these age groups compared to there being a decrease in smoking prevalence. Two major points are made in the rest of this section. The first is that the data in Table 4-8 demonstrates an increase in smoking cessation, between the ages of 20-24 and 40-44, that was considerably greater for the 1951-1955 birth cohort (43%) as compared to the 1926-1930 birth cohort (19%). This increased cessation between the ages of 20-24 and 40-44 is much larger than the change in smoking prevalence as calculated by Burns, et al. The second point is that in later years (1996 as compared to 1980) one-third of smokers had started to smoke only after age 19, as compared to only 14% of smokers in the earlier year. Smokers who start to smoke only after age 19 would not be expected to greatly contribute to the lung cancer death rate at ages 40-44.

There is little point in attempting to critique this particular analysis, in that there are numerous problems. Although the concepts that Burns, et al., advance may indeed play some role in the observed decrease in lung cancer death rates, it is impossible to determine what role they may play when Burns, et al., simply use an "example calculation" looking at only two birth cohorts at only two time periods. One cannot generalize such a calculation to all of the data. Secondly, Burns, et al., calculate percentages of both the increase in early cessation and the increase in late initiation on a constant population. Changes in population occur, and therefore percentage increases must be normalized to a constant population as is the case for lung cancer death rates.

It should also be pointed out that using the year 1996 as the second point in his late smoking initiation calculation is rather meaningless, since no lung cancer death rate data will be available for quite some time that deal with individuals who were 20-24 years of age in 1996.

The concluding paragraph of this section clarifies its goals:

> "In summary, a combination of the decline in smoking prevalence and the increase in late initiation of smoking could explain the excess decline in lung cancer death rates observed in the United Kingdom. These considerations should be part of an examination of the dramatic decline over time in lung cancer death rates at younger males in the U.K. The changes in lung cancer death rates in the United States appear to be consistent with changes in smoking prevalence."

There can be no question that a decline in smoking prevalence, including an increase in cessation, contributed to the decline in lung cancer death rates in the UK. However, as was pointed out above, even when these factors have been considered (Peto, et al., 2000; Lee and Forey, 1998), the decline in lung cancer death rates in the UK is still more rapid than could be accounted for by these factors alone. This suggests a role of a less hazardous product as well, which can only be a low-yield cigarette.

T. Matching U.S. Smoking Rates to U. S. Lung Cancer Death Rates

The goal of this section is to use a variation of the Doll, Peto model (Doll and Peto, 1978) in order to model the relationship of US smoking prevalence to US lung cancer death rate. The baseline lung cancer mortality data are taken from CPS-I. Predicted national rates can then be compared with the actual observed US mortality rates over time to evaluate whether the risks of smoking measured during the period 1960-1972 (CPS-I) continue to: (i) predict current lung cancer death rates, (ii) overestimate lung cancer rates over time suggesting a decline in the risk of smoking as the cigarettes smoked had lower machine-measured yields, or (iii) underestimate lung cancer rates over time as suggested by the comparison of the risks of smoking in CPS-I and CPS-II. If the last result is obtained, Burns, et al., suggest that one can conclude that smoking has not become less hazardous over time and may have become more hazardous.

Burns, et al., obtained smoking prevalence from the National Health Interview Survey data. The form of the Doll, Peto model that Burns used, obtained from the best fit of the CPS-I data was:

$$\text{lung cancer death rate} = K(\text{cigarettes/day} + 6)^{x}(\text{duration} - 3.5)^{y}$$

where $K = 1.7196 \times 10^{-10}$, $x = 0.85$, and $y = 3.71$. Although the form of this equation is identical to the Doll, Peto model, the constants are quite different. It is clearly beyond the scope of this review to attempt to critique this model. Smoking duration and cigarettes/day estimates were determined as follows:

> "Lung cancer death rates were calculated for each single year of age of initiation (which, when subtracted from age, yields duration of smoking) within each birth cohort for current smokers. The mean value for cigarettes smoked per day for all white male smokers in the National Health Interview Survey (16.45) was used as the term for cigarettes per day. The weighted sum of all the rates for individual ages of initiation yields the rate for the smokers in the cohort."

Lung cancer death rates for both former smokers and non-smokers were calculated as well, and a total lung cancer death rate was calculated for white males.

Actual observed lung cancer mortality rates by birth cohort were obtained from US mortality data, and are those presented by Mannino, et al. (2001). Lung cancer death rates estimated from

application of the model to smoking prevalence and CPS-I risk data were scaled to the actual US mortality rates. There was excellent agreement between the CPS-I predicted rates and the real US lung cancer death rates in each cohort until the late 1970's. However, beginning in 1979 and in later years, there was a progressive underestimation of US lung cancer mortality when the dose and duration risk relationships from CPS-I and US smoking prevalence by birth cohort were used to estimate lung cancer death rates. The authors state that these analyses suggest, if anything, that there has been an increase rather than a decrease in the carcinogenicity of smoking over the last several decades in the US. This information is shown graphically in Fig. 4-18a-i.

Burns, et al., also attempt to incorporate year-by-year tar average tar levels into this model. A term proportional to the sales-weighted tar yield of US cigarettes for each calendar year was applied to the predicted rates as *c* times the tar value, and the optimum value for *c* was determined. The resultant tar-adjusted rates were tested to determine whether the addition of the term to the predicted rates improved the goodness of fit of the predicted data to the observed US lung cancer mortality rates by cohort. Burns, et al., point out that the fit of the CPS-I predicted rates was improved by the addition of the tar term, but that the improved fit was in the direction of declining tar values increasing the risk. The conclusion reached in Chapter 4 is that regarding this calculation is:

> "The fit of the CPS-I predicted rates was improved by the addition of the tar term, but the improved fit was in the direction of declining tar values increasing the risk."

Although the quote above does not actually state that lowering tar increased the risk of lung cancer, it would not be at all surprising if the statement were interpreted by the average reader in just that manner. Is such an interpretation justified? In order to answer that question, it is essential to know exactly what procedure Burns, et al., used to incorporate tar into the model. This information is not contained within Chapter 4, so that it will be necessary to try and 'guess' at the most likely methodology he would have used. The best 'guess' is that Burns, et al., carried out a simple regression to see how tar yield related to the difference between the modeled and the actual lung cancer mortality rates, with *c* the slope of this regression line. Then, extending their model, using the calculated slope of the regression line (*c*) to include a tar term improved the fit, but was in the direction of "declining tar values increasing the risk." If the methodology described above was the methodology actually used by Burns, et al., the observed result was a foregone conclusion; that is, this calculation tells one nothing that was not already obvious. Since we know that US lung cancer rates rose more rapidly between 1960 and 1988 than would have been expected based on CPS-I data (comparison of CPS-II to CPS-I, Mannino, et al., 2000), and since we know that during that same period of time sales-weighted tar averages were declining in the US, than it is obvious that this calculation would suggest that the decline in tar was associated with increasing the risk. However, this is simply an example of an ecological association. For example, it was also known that the growth of the US suburban population was increasing during this period of time. One could equally well state that this population growth was associated with an increase in lung cancer risk.

Burns, et al., conclude this section as follows:

> "In these analyses, tar is a surrogate for the overall changes in cigarette design and manufacture over the last five decades, rather than a specific measure of the actual tar intake by the smoker. This analytic approach is an attempt to answer the question of whether the sum total of the changes occurring in cigarette design and composition over the last 45 years produced a reduction in carcinogenicty of smoking, and there appears to be little evidence for a population effect in the direction of a reduced risk. Moreover, this analysis supports the comparison of the two American Cancer Society prospective mortality studies (CPS-I and CPS-II) in suggesting that cigarette smoking may have become more, rather than less, hazardous, based on the cumulative effects of all the

changes in cigarette design and manufacture that have occurred over the last half century."

This conclusion is not surprising. First of all, as Burns, et al, point out, it is completely consistent with the comparative results, already discussed in considerable detail, between CPS-I and CPS-II. Secondly, the results are completely consistent with conclusions reached by Lee and Forey (1996) based on a much more detailed analysis of US lung cancer mortality time trends. Moreover, these results are also in agreement with data and conclusions presented by Mannino, et al. (2001), which Burns, et al., have cited a number of times. All three of these results, however, have not examined the most current situation in the US. For example, the analysis that Burns, et al., have carried out in this section are valid only through 1989, as can be seen from inspection of Figures 4-18 a-i. The analysis of Lee and Forey (1996) utilized data through 1985. Although Mannino, et al., utilized data through 1994, the results were presented in graphical form, making it very difficult to draw quantitative conclusions. However, inspection of the graph (Figure 2 in Mannino, et al.) that plots lung cancer mortality per 100,000 current or recent smokers vs. five-year birth cohort that provides relationships for both men and women as a function of smoking duration reveals what appears to be a downward trend in lung cancer mortality for smoking durations of 15, 20, and 25 years (implying younger smokers) for the most recent birth cohorts. Moreover, inspection of Table 4-9 in Chapter 4 also suggests that for the most recent data included in the table that lung cancer death rates are declining more rapidly than declines in smoking prevalence for younger smokers. As a consequence of these last two points, it was decided to undertake a relatively simple analysis of recent lung cancer death rates in the US as a function of smoking prevalence.

Lung cancer death rates in five-year periods (1951-1955 through 1991-1995) were plotted vs. five-year age groups (30-34 through 80-84) for five-year birth cohorts (1871-1875 through 1961-1965). Lung cancer death rates were obtained from WHO data. Plots were constructed for males, females, and both sexes combined. As an index of cigarette consumption, we used the average consumption of manufactured cigarettes per day from age 15-19 to the period in question, based on data going back to 1920 (Forey, et al., 2002). (This analysis assumes that consumption per head in any year is invariant of age, when it clearly is not. If one is comparing estimates for the same age at different times, variation by age may not matter much if the variation is similar at the various time points being compared. However, this assumption may not also be true. As smoking became fashionable, first among men, than among women, it is likely to have been in the first place taken up by younger adults, with the proportion of older smokers increasing over time. However, when looking at young age groups and recent periods, the main results of interest in this analysis, this problem is not likely to be too serious.) As this analysis focused primarily on the younger age groups, trends in lung cancer mortality for both sexes combined were compared to trends in cigarette consumption, unadjusted for tar, over time for age groups 35-39, 40-44 and 45-49. Sexes combined mortality data have been used, since the consumption data are sales-based and therefore relate to both sexes combined. This comparison shows that between 1976-80 and 1991-95, average unadjusted consumption has fallen 13%, 10% and 6% for age groups 35-39, 40-44 and 45-49, respectively, and the corresponding declines in lung cancer mortality have been 28%, 37%, and 28%. A comparison was also carried out using tar-adjusted consumption for the same age groups and time period. This comparison shows two distinct patterns very clearly. Firstly, in the period up to 1976-1980, the rise in lung cancer death rate has been substantially greater than the rise in consumption. This result is not only consistent with the conclusions reached by the now thoroughly discussed comparison between the American Cancer Society studies, CPS-I and CPS-II, but is also consistent with the published results of Lee and Forey (1996), which used more sophisticated model-fitting. Second, for the period from 1976-1980 through 1991-1995 the declines in average lung cancer mortality (28%, 37% and 28% for the three age groups) are slightly less then the declines in average tar adjusted consumption per head per day (respectively, 42%, 41% and 36%). It is extremely important to emphasize that the fact that lung cancer death rates declined at a somewhat slower rate for these age groups than did tar-adjusted consumption does not mean that reduced-delivery cigarettes are more hazardous than non-reduced-delivery cigarettes. If there was a 1:1 relationship between the extent of tar reduction

in reduced-delivery cigarettes and lung cancer mortality, one would expect a 1:1 relationship between the decline in tar-adjusted compensation and lung cancer death rates. The fact that the lung cancer death rate is intermediate between the unadjusted decline in consumption and the tar-adjusted decline in consumption is consistent with tar reduction having a role in the reduction in lung cancer death rates, as would be predicted by case-control and cohort studies, but with some compensation having occurred.

If indeed the analysis that we have carried out on recent lung cancer mortality trends in the US that strongly suggest a role of tar reduction in reduction of US lung cancer death rates, the legitimate question can be raised, has this phenomenon been noted by any other analysis? The answer to this question is affirmative, and this analysis was published in 2001 by Jemal, et al. Jemal, et al., analyzed lung cancer death rates through 1997. The methodology that they used was through the analysis of maximum likelihood estimates of calendar-period effects for age-period-cohort analysis of lung cancer mortality data. This methodology is rather complicated and as a consequence a full analysis of this publication is presented in Appendix B. The conclusions of Jemal, et al., however are as follows:

> "Cigarette smoking affects both early and late stages of the carcinogenic process. The effect of reducing tobacco carcinogen exposure on the late stage will be seen soon after the change in exposure. Thus, the generally convex shape of the calendar-period effect curves from 1970 through 1990 (Fig. 4) likely reflects the impact of the steadily improving trends in both carcinogen exposure from cigarettes (evidenced by the sharp decline in tar and nicotine yield) and smoking cessation over the study period (Fig. 5) on the late stage event. In contrast, the effect of reducing tobacco carcinogen exposure on the initiation event will not be observed for decades. The largest decreases in tar and nicotine yield and increases in smoking cessation rates occurred in the 1960s and 1970s. The sharp decline in calendar-period risk around 1990 may reflect the impact on the initiation stage of the decrease in tobacco carcinogen exposure and the increase in smoking cessation beginning around 1960; if so, the impact became manifest only after a latency period of approximately 30 years."

Thus Jemal, et al. present data that they interpret as showing a role or reduced-delivery cigarettes in reduction of lung cancer death rates in the US. It should be noted that the conclusions that Jemal, et al., present do not distinguish between the contribution of "carcinogen exposure" and increasing smoking cessation. If possible an analysis of their data will be carried out to determine if contributions from these two factors can be quantified.

The conclusions of the very long analysis contained in this section of Chapter 4 can be presented as follows:

1. There is ample evidence to show that lung cancer mortality rates in the US have increased over the period 1960 to 1980 and that these increases exceed projections based on cigarette smoking prevalence irrespective of whether or not reduced-delivery cigarettes have an impact on lung cancer mortality. This trend is confirmed by the analysis that Burns, et al., have carried out in this section, by comparison of CPS-I to CPS-II, and by the modeling work of Lee and Forey (1996). The reasons for this increase remain unknown.

2. More recent data on lung cancer mortality in the US (after ca. 1985) show rapid declines that exceed projections based on smoking prevalence. This can be seen not only from our own analysis, presented above, but even from inspection of Table 4-9 in Chapter 4, although numerous assumptions must be made. The publication by Jemal, et al., tends to confirm this conclusion, although it is not currently possible to determine the separate contributions of smoking cessation and tar reduction to the decreases in lung cancer mortality that Jemal, et al., observed. Nevertheless, there seems to be

accumulating evidence that in the US, as in the UK and Australia, that the effect of cigarette tar reduction on lung cancer mortality rates is becoming evident.

U. Summary

Burns, et al., summarize Chapter 4 as follows:

> "The three lines of evidence on lung cancer risk in relation to changes in cigarette design provide somewhat inconsistent findings, perhaps reflecting methodological limitations and the number of studies available. Detailed examination of lung cancer rates by age in the United States and the United Kingdom provide seemingly conflicting patterns from the two countries. Lesser risks for more recent cigarettes are one potential explanation for the rapid decline of lung cancer mortality at younger ages in the United Kingdom over recent years. However, the temporal pattern of lung cancer morality at younger ages in the United States is not consistent with this explanation. The temporally cross-sectional findings from several case-control and cohort studies provide some evidence of reduced risk for smokers of lower yield products at time points across the 1960s through the 1980s. These studies, however, provide only relative comparisons of risk and data analysis methods raise concern about biased findings in some. Finally, both the British Physician's study and the CPS I and II studies provide powerful evidence that both relative and absolute risks of lung cancer in smokers have risen from the 1950s through the 1980s. The different findings across these three lines of epidemiological evidence cannot be reconciled with available information. Overall, however, they do not provide evidence that public health has benefited from changes in cigarette design and manufacture of the last fifty years."

Let us look at the evidence, as presented in the review point by point.

1. Case-control and cohort studies clearly show a reduced lung cancer risk for low-yield cigarettes. Forty-two studies that compared lung cancer relative risk for filter compared to non-filter cigarettes found a reduction in lung cancer risk of 36% with no adjustment for cigarettes per day. Adjustment for cigarettes per day (33 studies) made essentially no difference, leading to a reduction of lung cancer risk of 35%. Results are similar for studies that compared low-tar to high-tar cigarette smokers. A total of 15 such studies found a reduction of 28% in lung cancer risk for smokers of low-tar cigarettes compared to smokers of higher-tar cigarettes when unadjusted for cigarettes per day. Studies adjusted for cigarettes per day (21) showed a reduction in risk of 25%. These results not only strongly confirm a reduction in risk for low-yield cigarettes, but also demonstrate that the observed reduction in risk is not the result of adjustment for cigarettes per day.

2. Analyses of lung cancer mortality trends over time lead to conflicting results. Evidence has been published for the UK (Peto, et al., 2000) and for Australia (Blizzard and Dwyer, 2001) that suggest that for young men in the UK and for young women in Australia, the use of low-yield cigarettes clearly plays a role in the observed decrease in lung cancer mortality rates for these groups of smokers. Published data, as well as the analysis carried out in Chapter 4 show, however, that lung cancer rates in the US, through about 1985, have been increasing at a more rapid rate than would be predicted through changes in smoking prevalence. Analysis of more recent data, however, tend to show that in the US, as in the UK and in Australia, lung cancer mortality rates are declining more rapidly than smoking cessation rates, strongly suggesting an influence of low-yield cigarettes on lung cancer mortality rates in the US as well.

3. The British Physicians Study cannot be said to provide "powerful evidence that both relative and absolute risks of lung cancer in smokers have risen from the 1950s through the 1980s." Aside from the fact that the second 20 years of follow up of a single cohort is not

representative of the total smoking population, a point made by Burns, et al., themselves, the increase in lung cancer relative risk was only 19%, and this increase is most likely due to the lack of adjustment for changes in smoking duration and daily cigarette consumption. This latter point was clearly made by Peto, et al., (2000). Clearly the same cannot be said for the comparison of CPS-I and CPS-II, since even with adjustments for cigarettes per day, CPS-II shows significantly higher relative risks than did CPS-I (a 50% increase for males and a 150% increase for females). However it is important to point out that the results for CPS-I and CPS-II are simply another way of assessing the temporal lung cancer mortality trends in the US already mentioned in 2 above. Moreover, both CPS-I and CPS-II clearly show a reduced relative risk for filter smokers compared to non-filter smokers, and the results were the same whether or not adjusted for cigarettes per day. Lastly, the increase of CPS-II compared to CPS-I does not truly provide any information as to whether or not there is a decrease in lung cancer risk for filter cigarette smokers.

Consequently, it is clear that ALL epidemiological evidence supports the biologically plausible assumption that at least most smokers of low-yield cigarettes will be at reduced risk for at least lung cancer. Clearly the most impressive support comes from the case-control and cohort studies that have attempted to compare relative risks for lung cancer for smokers of filter (or low-tar) cigarettes to smokers of non-filter (or high-tar) cigarettes. Evidence from national mortality statistics is suggestive, but not yet well established. Lastly, evidence from the British Physicians Study and comparison of CPS-II and CPS-I is actually not relevant. It is important to note, however, that the fact that the relative risk for reduction in lung cancer must be considered to be a weak association, and the fact that only recently have any changes in lung cancer death rates been observable indicates that although the evidence is highly suggestive, definitive proof cannot be said to have been established.

There are two other points that should be included in the summary of this review. The first deals with an issue that Burns, et al., raise several times in Chapter 4, but never develop. On page 74 they state:

> "Smokers of low-yield cigarettes may differ from smokers of high-yield cigarettes in important characteristics other than the cigarette smoked. These differences need to be carefully considered in epidemiological studies in order to prevent these other characteristics from introducing confounding facts that may bias the results of these studies. If low-yield cigarette smokers have lower intensities of smoking, are more likely to quit smoking, or have other characteristics that lower their disease risks, then differences in disease risks demonstrated between populations of high- and low-yield cigarette smokers may not be due to the differences in the cigarette that they smoke. These differences can be considered as confounding, as they relate to differences between high- and low-yield cigarette smokers reflecting the differences between those selecting and not selecting the product."

The issue of confounding, as anyone with any experience in the field of epidemiology knows full well, is always of concern. If we look at the relative risk comparing filter and non-filter smokers in the opposite sense, that is comparing non-filter to filter, the relative risk is about 1.6. This relative risk falls within the range generally considered to be weak, and confounding must be a concern. As pointed out earlier in this review, the burden of establishing that confounding may be responsible for all or part of a given relative risk should be placed on those individuals claiming a role of such confounding. Clearly, Burns, et al., have not been able to establish the potential role of the confounding factors indicated above, but relevant data would be most difficult to obtain. On the other hand, it is important to not dismiss the possibility of confounding out of hand. It should be noted, however, that the reduction in risk for lung cancer associated with reduction in cigarette tar delivery is clearly biologically plausible, and most of those studies that have attempted to investigate dose-response relationships have indeed found a relationship between decreasing level of tar and decreased risk for lung cancer. Moreover, although the meta-analytic relative risk

for lung cancer shows considerable heterogeneity, most of those causes of heterogeneity suggest restriction of the meta-analysis to studies where heterogeneity would have been reduced would have also reduced the pooled relative risks. One potential approach to defining the importance of confounding may be in designing a study to provide additional epidemiological data, which will be discussed in the next paragraph.

The second point deals with the next to the last sentence of the summary by Burns et al:

> "The different findings across these three lines of epidemiological evidence cannot be reconciled with available information."

We completely agree with this statement. Two areas in which we would like to recommend further studies are as follow:

1. Considerable discussion was devoted to analyses of more recent data with respect to trends in lung cancer death rates in the US which utilize the most recent data available. Although this review points out that there is at least suggestive evidence that the recent data support a role of cigarette tar reduction with respect to declines in lung cancer mortality, there is more work that needs to be done in this area.

2. There are essentially no data for very low-yield cigarettes. It is quite possible that such data would provide a very clear indication of a reduced risk related to a reduction in tar. Moreover, it is also likely that the relative risk associated with such cigarettes would be sufficiently large that the possibility of confounding would assume considerably less importance. Such a study would be both long and expensive; however, we recommend it as being essential. Initial steps to conduct such a study are already under way.

V. Conclusions

The conclusions for Chapter 4 are listed below, followed by this review's comments.

> 1. "Changes in cigarette design and manufacturing over the last fifty years have substantially lowered the sales-weighted, machine-measured tar and nicotine yields of cigarettes smoked in the United States."
>
> This statement is clearly corroborated by considerable data and requires no further comment.
>
> 2. "Cigarettes with low machine-measured yields by the FTC method are designed to allow compensatory smoking behaviors that enable a smoker to derive a wide range of tar and nicotine yields from the same brand, offsetting much of the theoretical benefit of a reduced-yield cigarette."
>
> It is clearly correct that smokers can derive a wide range of tar and nicotine yields from the same brand. This review does not agree that such a design is incorporated expressly into low-yield cigarettes but rather that technology does not exist, for conventional cigarettes, to design a cigarette that would not allow such compensatory smoking behavior.
>
> 3. "Existing disease risk data do not support making a recommendation that smokers switch cigarette brands. The recommendation that individuals who cannot stop smoking should switch to low yield cigarettes can cause harm if it misleads smokers to postpone serious efforts at cessation."

There is no question that the most effective way for a smoker to reduce his risk is to quit smoking. The issue as to whether more harm is caused if smokers who continue to smoke utilize a more hazardous product or if smokers postpone serious efforts to quit because of the existence of a less-hazardous product is clearly difficult to resolve. Moreover, resolving such an issue is clearly beyond the scope of this review.

4. "Widespread adoption of lower yield cigarettes by smokers in the United States has not prevented the sustained increase in lung cancer among older smokers."

This statement is clearly supported by existing data, but not at all surprising. Since older smokers would have spend a great part of their smoking experience with higher yield cigarettes, it is highly likely that switching to lower tar cigarettes late in life would have little measurable reduction in risk.

5. "Epidemiological studies have not consistently found lesser risk of diseases, other than lung cancer, among smokers of reduced yield cigarettes. Some studies have found lesser risks of lung cancer among smokers of reduced yield cigarettes. Some or all of this reduction in lung cancer risk may reflect differing characteristics of smokers of reduced-yield compared to higher-yield cigarettes."

The authors of this chapter did not carry out a quantitative analysis of the data that they tabulated for the association of reduced-delivery cigarettes with either cardiovascular disease or with chronic respiratory disease. These analyses were carried out as part of this review. The reduction in cardiovascular disease (fixed-effects meta-analysis) is 13% (statistically significant) whether adjusted or unadjusted cigarettes per day. Although this reduction is clearly less than was found for lung cancer, as was pointed out in Section H, the inverse relationship between smoking-related cardiovascular disease and age may have led to an understatement of risk reduction. A risk reduction (fixed-effects meta-analysis) of 30% (statistically significant) was calculated for the association of reduced-delivery cigarettes with respiratory disease. However, that calculation was based on a limited number of studies, and there appears to be a qualitative difference between results for chronic bronchitis and emphysema/COPD. With respect to lung cancer, it would be more accurate to say that most studies have found lesser risks of lung cancer among smokers or reduced yield cigarettes, as well as stating that all studies pooled demonstrate a 25-35% in risk. As far as the third point is concerned, this review has clearly shown that changes in cigarettes per day do not account for the observed reduction in lung cancer risk associated with lower-yield cigarettes. There is insufficient evidence to either establish or to rule out the existence of other confounding factors, although it seems unlikely that such factors could account for the observed reduction in risk.

6. "There is no convincing evidence that changes in cigarette design between 1950 and the mid 1980s have resulted in an important decrease in the disease burden caused by cigarette use either for smokers as a group or for the whole population."

This statement is consistent with US data through approximately 1985. Analysis of more recent data suggest that US lung cancer mortality are declining more rapidly than would be predicted from smoking prevalence data, at least for younger smokers. Recent published data for the only other two countries where relevant studies have been published; namely, the UK and Australia, also support a role for reduced-delivery cigarettes with respect to reduction of lung cancer risk.

It is worth pointing out that these conclusions seem to be quite mild compared to the tenor of Chapter 4 itself. This review will not speculate as to the possible reason for this.

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